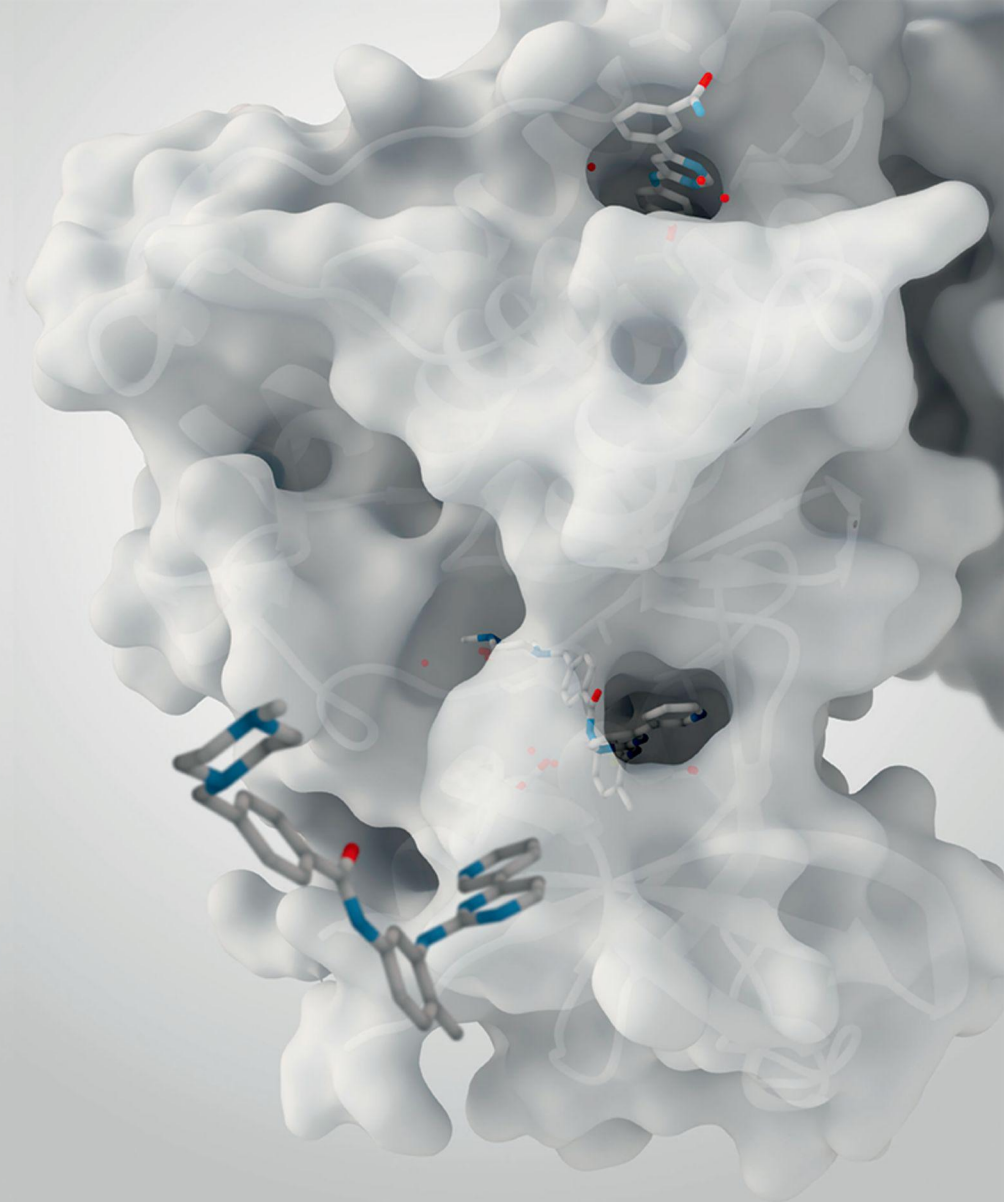


OXFORD



an introduction to

# MEDICINAL CHEMISTRY

GRAHAM L. PATRICK

sixth edition

## **An Introduction to Medicinal Chemistry**



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# MEDICINAL CHEMISTRY

sixth edition

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# 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 five editions, as well as useful feedback from readers, there has been some reorganization and updating of chapters, especially those in section E. A chapter on cardiovascular agents has also been added.

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

- Part A contains five 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, i.e. QSAR, combinatorial synthesis, and computer-aided design.
- Part E covers a selection of specific topics within medicinal chemistry—antibacterial, antiviral, and anticancer agents, cholinergics and anticholinesterases, adrenergics, opioid analgesics, anti-ulcer agents, and cardiovascular 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 anti-ulcer 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), kinase inhibitors as anticancer agents (Chapter 21), and the statins as cholesterol-lowering agents (Case study 1) are prime examples of the modern approach.

G. L. P.  
December 2016

# About the book

The sixth edition of *An Introduction to Medicinal Chemistry* and its accompanying companion website contains many learning features. This section illustrates each of these learning features and explains how they will help you to gain a deeper understanding of this fascinating subject.

## Emboldened keywords

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

### Glossary

**3D QSAR** QSAR studies which relate the biological activities of a series of compounds to their steric and electrostatic fields determined by molecular modelling software.

**Abzyme** An antibody with catalytic properties.

**ADME** Refers to drug absorption, drug metabolism, and drug excretion.

**Adrenal medulla** A gland situated in the center of the adrenal gland.

**Adrenaline** A catecholamine neurotransmitter, and was the first hormone to be identified.

## Boxes

Boxes are used to present in-depth material and to explore how the concepts of medicinal chemistry are applied in practice.

### 582 Chapter 21 Anticancer agents

#### BOX 21.7 General synthesis of gefitinib and related analogues

A general synthesis for gefitinib and its analogues starts from a quinazolinone starting material which acts as the central scaffold for the molecule. The synthesis is then a case of introducing the two important substituents. Selective demethylation reveals a phenol which is then

subsequent reagents. Chloroformyl group, and the substituted by an aniline to substituent. Deprotection of the phenol with an alkyl halide into

## Key points

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

### KEY POINTS

- Pharmaceutical companies tend to concentrate on developing drugs for diseases which are prevalent in developed countries, and aim to produce compounds with better properties than existing drugs.
- A molecular target is chosen which is believed to influence a particular disease when affected by a drug. The greater the selectivity that can be achieved, the less chance of side effects.

Unfortunately, this complex process is often difficult and the compounds often come from their natural source—often a plant or animal. As a result, the process of designing simpler analogues is often a long and costly process.

Many natural products have complex structures which no chemist could design. For example, the structure of a natural product (Fig. 12.6) is a natural product with a complex, unstable looking trioxane ring system, which has appeared in nature.

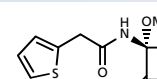
## Questions

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

### QUESTIONS

- How would you convert penicillin G to 6-aminopenicillanic acid (6-APA) using chemical reagents? Suggest how you would make ampicillin from 6-APA.
- Penicillin is produced biosynthetically from cysteine and valine. If the biosynthetic pathway could accept different amino acids, what sort of penicillin analogues might be formed if valine was replaced by alanine, phenylalanine,

- The following structure is a natural product. What sort of properties do you think it has?



## Further reading

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

### FURTHER READING

Abraham, D. J. (ed.) (2003) *Narcotic analgesics*. in *Burger's medicinal chemistry and drug discovery*, 6th edn. Chapter 7, John Wiley and Sons, New York.

Corbett, A. D., et al. (2006) 75 Years of opioid research: the exciting but vain quest for the Holy Grail. *British Journal of Pharmacology*, **147**, S153–62.

Pouletty, P. (2002) Drug addiction and medically treatable disorders. *Discovery*, **1**, 731–6.

Roberts, S. M., and Price, B. (2002) buprenorphine, a potent analgesic. *chemistry—the role of organic chemistry*. Chapter 7, Academic Press.

## Appendices

There are several appendices provided at the end of the book, providing further information which you may find useful. Appendix 1 shows the structures of common amino acids, with the standard genetic code given in Appendix 2. Statistical data for QSAR is provided in Appendix 3, while further information relating to the action of nerves, and microorganisms, are given in Appendices 4 and 5, respectively. Appendix 6 lists trade names and the drug(s) to which they correspond, while trade names corresponding to specific drugs in the main index are shown in brackets. Appendix 7 shows the likely hydrogen bonding interactions for different functional groups. Related appendices on the website give information on properties such as molecular weight, log *P*, the number of hydrogen bonding groups and rotatable bonds, molecular weight, and polar surface area for several clinically important drugs.

## Links

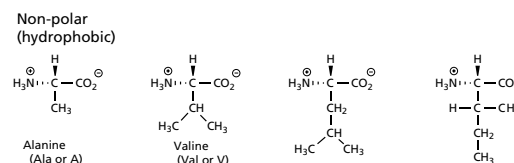
Links have been added to the text which alert the reader to relevant articles and molecular modelling exercises on the accompanying website for the textbook. These exercises involve the use of Spartan and/or ChemBio3D molecular modelling software, as well as Excel.

## Case Studies

Case Studies help you to link the underlying theory to its pharmaceutical applications and appreciate the real-world applications of the science.

### Appendix 1

#### Essential amino acids



An example of a 3D QSAR study is described in the case study in section 18.10.6.

For additional material see Web article 5: The design of a serotonin antagonist as a possible anxiolytic agent on the Online Resource Centre at [www.oxfordtextbooks.co.uk/orc/patrick6e/](http://www.oxfordtextbooks.co.uk/orc/patrick6e/)

#### 18.10.3 Advantages of CoMFA over traditional QSAR

easier to visualize than traditional QSAR. In CoMFA, the proper calculated individually. There is no reliance on molecular weight factors. There is no need to select molecules of similar structure. It is not necessary that all the compounds have similar pharmacophore and interact with the same target, they can all be active. The graphical representation of the beneficial interactions is more intuitive.

### CASE STUDY 9

#### Factor Xa inhibitors

##### CS9.1 Introduction

the susceptible peptide bond. The hydrophobic cleft contains a hydrophobic residue which is important for both binding and catalysis.



# 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, and designed to complement the textbook.

You will find the Online Resource Centre at:

[www.oxfordtextbooks.co.uk/orc/patrick6e/](http://www.oxfordtextbooks.co.uk/orc/patrick6e/)



## Student resources

### Multiple-choice questions

Self-test multiple-choice questions are available for each chapter allowing you to test your knowledge and understanding of key concepts as you progress through the book.

### Web articles

A series of articles have been placed on the web to enable you to read further into selected topics. These articles describe recent developments in the field and give further information on some of the topics covered in the book. Cross-references to these articles are provided at relevant points in the text.

### Molecular modelling exercises

A series of molecular modelling exercises have been added to the website aimed at students using Spartan or ChemBio3D molecular modelling software. Alerts are provided in the book to molecular modelling exercises related to specific topic areas.

### Journal Club

Suggested papers are provided along with questions and answer guidance, to help you to critically analyse the research literature.

## Assignments

Suggested assignments are provided to help you develop your analysis and problem-solving skills.

## Lecturer resources

For registered adopters of the book

### Test Bank

A bank of multiple-choice questions, with links to relevant sections in the book, which can be downloaded and customized for your teaching.

### Answers

Answers to end-of-chapter questions in the book.

### 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 accompany selected topics from the book.

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# Brief contents

List of boxes	xxvi	
Acronyms and abbreviations	xxviii	
1 Drugs and drug targets: an overview	1	
<b>PART A Drug targets</b>		
2 Protein structure and function	17	
3 Enzymes: structure and function	30	
4 Receptors: structure and function	44	
5 Receptors and signal transduction	61	
6 Nucleic acids: structure and function	77	
<b>PART B Pharmacodynamics and pharmacokinetics</b>		
7 Enzymes as drug targets	93	
8 Receptors as drug targets	109	
9 Nucleic acids as drug targets	128	
10 Miscellaneous drug targets	144	
11 Pharmacokinetics and related topics	162	
■ Case study 1: Statins	187	
<b>PART C Drug discovery, design, and development</b>		
12 Drug discovery: finding a lead	197	
13 Drug design: optimizing target interactions	223	
14 Drug design: optimizing access to the target	256	
15 Getting the drug to market	284	
■ Case study 2: The design of ACE inhibitors	302	
■ Case study 3: Artemisinin and related antimalarial drugs	309	
■ Case study 4: The design of oxamniquine	315	
<b>PART D Tools of the trade</b>		
16 Combinatorial and parallel synthesis	325	
17 Computers in medicinal chemistry	349	
18 Quantitative structure–activity relationships (QSAR)	395	
■ Case study 5: Design of a thymidylate synthase inhibitor	419	
<b>PART E Selected topics in medicinal chemistry</b>		
19 Antibacterial agents	425	
20 Antiviral agents	490	
21 Anticancer agents	543	
22 Cholinergics, anticholinergics, and anticholinesterases	620	
23 Drugs acting on the adrenergic nervous system	654	
24 The opioid analgesics	678	
25 Anti-ulcer agents	705	
26 Cardiovascular drugs	735	
■ Case study 6: Steroidal anti-inflammatory agents	766	
■ Case study 7: Current research into antidepressant agents	776	
■ Case study 8: The design and development of aliskiren	781	
■ Case study 9: Factor Xa inhibitors	788	
■ Case study 10: Reversible inhibitors of HCV NS3-4A protease	795	
Appendix 1 Essential amino acids	801	
Appendix 2 The standard genetic code	802	
Appendix 3 Statistical data for QSAR	803	
Appendix 4 The action of nerves	807	
Appendix 5 Microorganisms	811	
Appendix 6 Trade names and drugs	813	
Appendix 7 Hydrogen bonding interactions	822	
Glossary	824	
General further reading	845	
Index	847	



# Detailed contents

List of boxes	xxvi	3.5 The catalytic role of enzymes	32
Acronyms and abbreviations	xxviii	3.5.1 Binding interactions	32
<b>1 Drugs and drug targets: an overview</b>	<b>1</b>	3.5.2 Acid–base catalysis	33
1.1 What is a drug?	1	3.5.3 Nucleophilic groups	34
1.2 Drug targets	3	3.5.4 Stabilization of the transition state	35
1.2.1 Cell structure	3	3.5.5 Cofactors	35
1.2.2 Drug targets at the molecular level	4	3.5.6 Naming and classification of enzymes	37
1.3 Intermolecular bonding forces	5	3.5.7 Genetic polymorphism and enzymes	37
1.3.1 Electrostatic or ionic bonds	5	3.6 Regulation of enzymes	38
1.3.2 Hydrogen bonds	6	3.7 Isozymes	40
1.3.3 Van der Waals interactions	8	3.8 Enzyme kinetics	41
1.3.4 Dipole–dipole and ion–dipole interactions	8	3.8.1 The Michaelis–Menten equation	41
1.3.5 Repulsive interactions	9	3.8.2 Lineweaver–Burk plots	42
1.3.6 The role of water and hydrophobic interactions	10	Box 3.1 The external control of enzymes by nitric oxide	39
1.4 Pharmacokinetic issues and medicines	11	<b>4 Receptors: structure and function</b>	<b>44</b>
1.5 Classification of drugs	11	4.1 Role of the receptor	44
1.6 Naming of drugs and medicines	12	4.2 Neurotransmitters and hormones	44
		4.3 Receptor types and subtypes	47
		4.4 Receptor activation	47
		4.5 How does the binding site change shape?	47
		4.6 Ion channel receptors	49
		4.6.1 General principles	49
		4.6.2 Structure	50
		4.6.3 Gating	51
		4.6.4 Ligand-gated and voltage-gated ion channels	51
		4.7 G-protein-coupled receptors	52
		4.7.1 General principles	52
		4.7.2 Structure	53
		4.7.3 The rhodopsin-like family of G-protein-coupled receptors	53
		4.7.4 Dimerization of G-coupled receptors	55
		4.8 Kinase receptors	55
		4.8.1 General principles	55
		4.8.2 Structure of tyrosine kinase receptors	56
		4.8.3 Activation mechanism for tyrosine kinase receptors	56
		4.8.4 Tyrosine kinase receptors as targets in drug discovery	57
		4.8.4.1 The ErbB family of tyrosine kinase receptors	57
		4.8.4.2 Vascular endothelial growth factor receptors	58
		4.8.4.3 Platelet-derived growth factor receptor	58
		4.8.4.4 Stem cell growth factor receptor	58
		4.8.4.5 Anaplastic lymphoma kinase (ALK)	58
		4.8.4.6 The RET receptor	58
		4.8.4.7 Hepatocyte growth factor receptor or c-MET receptor	58
<b>PART A Drug targets</b>			
<b>2 Protein structure and function</b>	<b>17</b>		
2.1 The primary structure of proteins	17		
2.2 The 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 The tertiary structure of proteins	19		
2.3.1 Covalent bonds: disulphide 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 The 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	26		
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 catalyse reactions?	31		
3.3 The active site of an enzyme	31		
3.4 Substrate binding at an active site	32		

4.9	Intracellular receptors	59
4.10	Regulation of receptor activity	59
4.11	Genetic polymorphism and receptors	60
<b>5</b>	<b>Receptors and signal transduction</b>	<b>61</b>
5.1	Signal transduction pathways for G-protein-coupled receptors	61
5.1.1	Interaction of the receptor–ligand complex with G-proteins	61
5.1.2	Signal transduction pathways involving the $\alpha$ -subunit	62
5.2	Signal transduction involving G-proteins and adenylylase	63
5.2.1	Activation of adenylylase by the $\alpha_s$ -subunit	63
5.2.2	Activation of protein kinase A	64
5.2.3	The $G_i$ -protein	65
5.2.4	General points about the signalling cascade involving cyclic AMP	66
5.2.5	The role of the $\beta\gamma$ -dimer	66
5.2.6	Phosphorylation	66
5.3	Signal transduction involving G-proteins and phospholipase $C_\beta$	68
5.3.1	G-protein effect on phospholipase $C_\beta$	68
5.3.2	Action of the secondary messenger: diacylglycerol	68
5.3.3	Action of the secondary messenger: inositol triphosphate	68
5.3.4	Resynthesis of phosphatidylinositol diphosphate	70
5.4	Signal transduction involving kinase receptors	70
5.4.1	Activation of signalling proteins and enzymes	70
5.4.2	The MAPK signal transduction pathway	71
5.4.3	Activation of guanylate cyclase by kinase receptors	71
5.4.4	The JAK-STAT signal transduction pathway	72
5.4.5	The PI3K/Akt/mTOR signal transduction pathway	73
5.5	The hedgehog signalling pathway	74
<b>6</b>	<b>Nucleic acids: structure and function</b>	<b>77</b>
6.1	Structure of DNA	77
6.1.1	The primary structure of DNA	77
6.1.2	The secondary structure of DNA	77
6.1.3	The tertiary structure of DNA	80
6.1.4	Chromatins	82
6.1.5	Genetic polymorphism and personalized medicine	82
6.2	Ribonucleic acid and protein synthesis	82
6.2.1	Structure of RNA	82
6.2.2	Transcription and translation	83
6.2.3	Small nuclear RNA	85
6.2.4	The regulatory role of RNA	85
6.3	Genetic illnesses	85
6.4	Molecular biology and genetic engineering	87

## PART B Pharmacodynamics and pharmacokinetics

<b>7</b>	<b>Enzymes as drug targets</b>	<b>93</b>
7.1	Inhibitors acting at the active site of an enzyme	93
7.1.1	Reversible inhibitors	93
7.1.2	Irreversible inhibitors	94
7.2	Inhibitors acting at allosteric binding sites	96
7.3	Uncompetitive and non-competitive inhibitors	96
7.4	Transition-state analogues: renin inhibitors	97
7.5	Suicide substrates	98
7.6	Isozyme selectivity of inhibitors	99
7.7	Medicinal uses of enzyme inhibitors	99
7.7.1	Enzyme inhibitors used against microorganisms	99
7.7.2	Enzyme inhibitors used against viruses	101
7.7.3	Enzyme inhibitors used against the body's own enzymes	101
7.7.4	Enzyme modulators	103
7.8	Enzyme kinetics	104
7.8.1	Lineweaver–Burk plots	104
7.8.2	Comparison of inhibitors	106
Box 7.1	A cure for antifreeze poisoning	94
Box 7.2	Irreversible inhibition for the treatment of obesity	96
Box 7.3	Suicide substrates	100
Box 7.4	Designing drugs to be isozyme selective	101
Box 7.5	Action of toxins on enzymes	102
Box 7.6	Kinase inhibitors	104
<b>8</b>	<b>Receptors as drug targets</b>	<b>109</b>
8.1	Introduction	109
8.2	The design of agonists	109
8.2.1	Binding groups	109
8.2.2	Position of the binding groups	111
8.2.3	Size and shape	112
8.2.4	Other design strategies	112
8.2.5	Pharmacodynamics and pharmacokinetics	112
8.2.6	Examples of agonists	113
8.2.7	Allosteric modulators	113
8.3	The design of antagonists	114
8.3.1	Antagonists acting at the binding site	114
8.3.2	Antagonists acting outwith the binding site	117
8.4	Partial agonists	118
8.5	Inverse agonists	119
8.6	Desensitization and sensitization	119
8.7	Tolerance and dependence	121

8.8	Receptor types and subtypes	122	<b>11 Pharmacokinetics and related topics</b>	<b>162</b>	
8.9	Affinity, efficacy, and potency	124	11.1	The three phases of drug action	162
Box 8.1	An unexpected agonist	113	11.2	A typical journey for an orally active drug	162
Box 8.2	Estradiol and the estrogen receptor	116	11.3	Drug absorption	163
<b>9</b>	<b>Nucleic acids as drug targets</b>	<b>128</b>	11.4	Drug distribution	165
9.1	Intercalating drugs acting on DNA	128	11.4.1	Distribution round the blood supply	165
9.2	Topoisomerase poisons: non-intercalating	129	11.4.2	Distribution to tissues	165
9.3	Alkylating and metallating agents	131	11.4.3	Distribution to cells	165
9.3.1	Nitrogen mustards	132	11.4.4	Other distribution factors	165
9.3.2	Nitrosoureas	132	11.4.5	Blood–brain barrier	166
9.3.3	Busulfan	132	11.4.6	Placental barrier	166
9.3.4	Cisplatin	133	11.4.7	Drug–drug interactions	166
9.3.5	Dacarbazine and procarbazine	134	11.5	Drug metabolism	167
9.3.6	Mitomycin C	135	11.5.1	Phase I and phase II metabolism	167
9.4	Chain cutters	136	11.5.2	Phase I transformations catalysed by cytochrome P450 enzymes	167
9.5	Chain terminators	137	11.5.3	Phase I transformations catalysed by flavin-containing monooxygenases	170
9.6	Control of gene transcription	138	11.5.4	Phase I transformations catalysed by other enzymes	170
9.7	Agents that act on RNA	139	11.5.5	Phase II transformations	171
9.7.1	Agents that bind to ribosomes	139	11.5.6	Metabolic stability	172
9.7.2	Antisense therapy	139	11.5.7	The first pass effect	176
<b>10</b>	<b>Miscellaneous drug targets</b>	<b>144</b>	11.6	Drug excretion	176
10.1	Transport proteins as drug targets	144	11.7	Drug administration	177
10.2	Structural proteins as drug targets	144	11.7.1	Oral administration	178
10.2.1	Viral structural proteins as drug targets	144	11.7.2	Absorption through mucous membranes	178
10.2.2	Tubulin as a drug target	145	11.7.3	Rectal administration	178
10.2.2.1	Agents which inhibit tubulin polymerization	145	11.7.4	Topical administration	178
10.2.2.2	Agents which inhibit tubulin depolymerization	146	11.7.5	Inhalation	179
10.3	Biosynthetic building blocks as drug targets	147	11.7.6	Injection	179
10.4	Biosynthetic processes as drug targets: chain terminators	148	11.7.7	Implants	180
10.5	Protein–protein interactions	148	11.8	Drug dosing	180
10.6	Lipids as a drug target	152	11.8.1	Drug half-life	181
10.6.1	‘Tunnelling molecules’	152	11.8.2	Steady state concentration	181
10.6.2	Ion carriers	155	11.8.3	Drug tolerance	182
10.6.3	Tethers and anchors	156	11.8.4	Bioavailability	182
10.7	Carbohydrates as drug targets	157	11.9	Formulation	182
10.7.1	Glycomics	157	11.10	Drug delivery	183
10.7.2	Antigens and antibodies	158	Box 11.1	Metabolism of an antiviral agent	175
10.7.3	Cyclodextrins	160	<b>Case study 1: Statins</b>	<b>187</b>	
Box 10.1	Antidepressant drugs acting on transport proteins	145	■ <b>CS1.1 Cholesterol and coronary heart disease</b>	<b>187</b>	
Box 10.2	Targeting transcription factor–coactivator interactions	149	■ <b>CS1.2 The target enzyme</b>	<b>188</b>	
Box 10.3	Cyclodextrins as drug scavengers	159	■ <b>CS1.3 The discovery of statins</b>	<b>190</b>	
			■ <b>CS1.4 Mechanism of action for statins: pharmacodynamics</b>	<b>192</b>	
			■ <b>CS1.5 Binding interactions of statins</b>	<b>192</b>	
			■ <b>CS1.6 Other mechanisms of action for statins</b>	<b>193</b>	
			■ <b>CS1.7 Other targets for cholesterol-lowering drugs</b>	<b>194</b>	



## PART C Drug discovery, design, and development

<b>12 Drug discovery: finding a lead</b>	<b>197</b>		
12.1 Choosing a disease	197	Box 12.1 Recently discovered targets: the caspases	198
12.2 Choosing a drug target	197	Box 12.2 Pitfalls in choosing particular targets	200
12.2.1 Drug targets	197	Box 12.3 Early tests for potential toxicity	201
12.2.2 Discovering drug targets	197	Box 12.4 Selective optimization of side activities (SOSA)	213
12.2.3 Target specificity and selectivity between species	199	Box 12.5 Natural ligands as lead compounds	214
12.2.4 Target specificity and selectivity within the body	199	Box 12.6 Examples of serendipity	216
12.2.5 Targeting drugs to specific organs and tissues	200	Box 12.7 The use of NMR spectroscopy in finding lead compounds	217
12.2.6 Pitfalls	200	Box 12.8 Click chemistry <i>in situ</i>	219
12.2.7 Multi-target drugs	201		
12.3 Identifying a bioassay	203	<b>13 Drug design: optimizing target interactions</b>	<b>223</b>
12.3.1 Choice of bioassay	203	13.1 Structure–activity relationships	223
12.3.2 <i>In vitro</i> tests	203	13.1.1 Binding role of alcohols and phenols	224
12.3.3 <i>In vivo</i> tests	203	13.1.2 Binding role of aromatic rings	225
12.3.4 Test validity	204	13.1.3 Binding role of alkenes	226
12.3.5 High-throughput screening	204	13.1.4 The binding role of ketones and aldehydes	226
12.3.6 Screening by NMR	205	13.1.5 Binding role of amines	226
12.3.7 Affinity screening	205	13.1.6 Binding role of amides	228
12.3.8 Surface plasmon resonance	205	13.1.7 Binding role of quaternary ammonium salts	229
12.3.9 Scintillation proximity assay	206	13.1.8 Binding role of carboxylic acids	229
12.3.10 Isothermal titration calorimetry	206	13.1.9 Binding role of esters	230
12.3.11 Virtual screening	207	13.1.10 Binding role of alkyl and aryl halides	230
12.4 Finding a lead compound	207	13.1.11 Binding role of thiols and ethers	231
12.4.1 Screening of natural products	207	13.1.12 Binding role of other functional groups	231
12.4.1.1 The plant kingdom	207	13.1.13 Binding role of alkyl groups and the carbon skeleton	231
12.4.1.2 Microorganisms	208	13.1.14 Binding role of heterocycles	232
12.4.1.3 Marine sources	209	13.1.15 Isosteres	233
12.4.1.4 Animal sources	209	13.1.16 Testing procedures	234
12.4.1.5 Venoms and toxins	210	13.1.17 SAR in drug optimization	234
12.4.2 Medical folklore	210	13.2 Identification of a pharmacophore	235
12.4.3 Screening synthetic compound ‘libraries’	210	13.3 Drug optimization: strategies in drug design	236
12.4.4 Existing drugs	211	13.3.1 Variation of substituents	236
12.4.4.1 ‘Me too’ and ‘me better’ drugs	211	13.3.1.1 Alkyl substituents	236
12.4.4.2 Enhancing a side effect	211	13.3.1.2 Substituents on aromatic or heteroaromatic rings	237
12.4.5 Starting from the natural ligand or modulator	214	13.3.1.3 Synergistic effects	238
12.4.5.1 Natural ligands for receptors	214	13.3.2 Extension of the structure	239
12.4.5.2 Natural substrates for enzymes	214	13.3.3 Chain extension/contraction	239
12.4.5.3 Enzyme products as lead compounds	214	13.3.4 Ring expansion/contraction	239
12.4.5.4 Natural modulators as lead compounds	215	13.3.5 Ring variations	241
12.4.6 Combinatorial and parallel synthesis	215	13.3.6 Ring fusions	242
12.4.7 Computer-aided design of lead compounds	215	13.3.7 Isosteres and bio-isosteres	243
12.4.8 Serendipity and the prepared mind	215	13.3.8 Simplification of the structure	244
12.4.9 Computerized searching of structural databases	217	13.3.9 Rigidification of the structure	247
12.4.10 Fragment-based lead discovery	217	13.3.10 Conformational blockers	248
12.4.11 Properties of lead compounds	219	13.3.11 Structure-based drug design and molecular modelling	248
12.5 Isolation and purification	220	13.3.12 Drug design by NMR spectroscopy	250
12.6 Structure determination	220	13.3.13 The elements of luck and inspiration	250
12.7 Herbal medicine	220	13.3.14 Designing drugs to interact with more than one target	252
		13.3.14.1 Agents designed from known drugs	252
		13.3.14.2 Agents designed from non-selective lead compounds	253

Box 13.1	Converting an enzyme substrate to an inhibitor by extension tactics	240	14.7.2	Localizing a drug's area of activity	274
Box 13.2	Simplification	245	14.7.3	Increasing absorption	274
Box 13.3	Rigidification tactics in drug design	249	14.8	Endogenous compounds as drugs	274
Box 13.4	The structure-based drug design of crizotinib	251	14.8.1	Neurotransmitters	274
<b>14</b>	<b>Drug design: optimizing access to the target</b>	<b>256</b>	14.8.2	Natural hormones, peptides, and proteins as drugs	275
14.1	Optimizing hydrophilic/hydrophobic properties	256	14.8.3	Antibodies as drugs	276
14.1.1	Masking polar functional groups to decrease polarity	257	14.9	Peptides and peptidomimetics in drug design	277
14.1.2	Adding or removing polar functional groups to vary polarity	257	14.9.1	Peptidomimetics	278
14.1.3	Varying hydrophobic substituents to vary polarity	257	14.9.2	Peptide drugs	280
14.1.4	Variation of <i>N</i> -alkyl substituents to vary $pK_a$	258	14.10	Oligonucleotides as drugs	280
14.1.5	Variation of aromatic substituents to vary $pK_a$	258	Box 14.1	The use of bio-isosteres to increase absorption	259
14.1.6	Bio-isosteres for polar groups	258	Box 14.2	Shortening the lifetime of a drug	264
14.2	Making drugs more resistant to chemical and enzymatic degradation	259	Box 14.3	Identifying and replacing potentially toxic groups	267
14.2.1	Steric shields	259	Box 14.4	Varying esters in prodrugs	269
14.2.2	Electronic effects of bio-isosteres	259	Box 14.5	Prodrugs masking toxicity and side effects	271
14.2.3	Steric and electronic modifications	260	Box 14.6	Prodrugs to improve water solubility	272
14.2.4	Metabolic blockers	260	<b>15</b>	<b>Getting the drug to market</b>	<b>284</b>
14.2.5	Removal or replacement of susceptible metabolic groups	261	15.1	Preclinical and clinical trials	284
14.2.6	Group shifts	261	15.1.1	Toxicity testing	284
14.2.7	Ring variation and ring substituents	262	15.1.2	Drug metabolism studies	285
14.3	Making drugs less resistant to drug metabolism	263	15.1.3	Pharmacology, formulation, and stability tests	287
14.3.1	Introducing metabolically susceptible groups	263	15.1.4	Clinical trials	287
14.3.2	Self-destruct drugs	263	15.1.4.1	Phase I studies	288
14.4	Targeting drugs	264	15.1.4.2	Phase II studies	288
14.4.1	Targeting tumour cells: 'search and destroy' drugs	264	15.1.4.3	Phase III studies	289
14.4.2	Targeting gastrointestinal infections	265	15.1.4.4	Phase IV studies	289
14.4.3	Targeting peripheral regions rather than the central nervous system	265	15.1.4.5	Ethical issues	290
14.4.4	Targeting with membrane tethers	265	15.2	Patenting and regulatory affairs	291
14.5	Reducing toxicity	266	15.2.1	Patents	291
14.6	Prodrugs	266	15.2.2	Regulatory affairs	293
14.6.1	Prodrugs to improve membrane permeability	267	15.2.2.1	The regulatory process	293
14.6.1.1	Esters as prodrugs	267	15.2.2.2	Fast tracking and orphan drugs	294
14.6.1.2	<i>N</i> -Methylated prodrugs	268	15.2.2.3	Good laboratory, manufacturing, and clinical practice	294
14.6.1.3	Trojan horse approach for transport proteins	268	15.2.2.4	Analysis of cost versus benefits	295
14.6.2	Prodrugs to prolong drug activity	269	15.3	Chemical and process development	295
14.6.3	Prodrugs masking drug toxicity and side effects	270	15.3.1	Chemical development	295
14.6.4	Prodrugs to lower water solubility	270	15.3.2	Process development	297
14.6.5	Prodrugs to improve water solubility	270	15.3.3	Choice of drug candidate	299
14.6.6	Prodrugs used in the targeting of drugs	271	15.3.4	Natural products	299
14.6.7	Prodrugs to increase chemical stability	272	Box 15.1	Drug metabolism studies and drug design	286
14.6.8	Prodrugs activated by external influence (sleeping agents)	273	Box 15.2	Synthesis of ebalzotan	296
14.7	Drug alliances	273	Box 15.3	Synthesis of ICI D7114	297
14.7.1	'Sentry' drugs	273	<b>Case study 2: The design of ACE inhibitors</b>	<b>302</b>	
			Box CS2.1	Synthesis of captopril and enalaprilat	307
			<b>Case study 3: Artemisinin and related antimalarial drugs</b>	<b>309</b>	
			■ CS3.1	Introduction	309
			■ CS3.2	Artemisinin	309
			■ CS3.3	Structure and synthesis of artemisinin	310

■ CS3.4 Structure–activity relationships	310	17 Computers in medicinal chemistry	349
■ CS3.5 Mechanism of action	311	17.1 Molecular and quantum mechanics	349
■ CS3.6 Drug design and development	313	17.1.1 Molecular mechanics	349
Box CS3.1 Clinical properties of artemisinin and analogues	313	17.1.2 Quantum mechanics	349
Case study 4: The design of oxamniquine	315	17.1.3 Choice of method	350
■ CS4.1 Introduction	315	17.2 Drawing chemical structures	350
■ CS4.2 From lucanthone to oxamniquine	315	17.3 3D structures	350
■ CS4.3 Mechanism of action	319	17.4 Energy minimization	351
■ CS4.4 Other agents	319	17.5 Viewing 3D molecules	351
Box CS4.1 Synthesis of oxamniquine	320	17.6 Molecular dimensions	353
		17.7 Molecular properties	353
		17.7.1 Partial charges	353
		17.7.2 Molecular electrostatic potentials	354
		17.7.3 Molecular orbitals	355
		17.7.4 Spectroscopic transitions	355
		17.7.5 The use of grids in measuring molecular properties	356
		17.8 Conformational analysis	358
		17.8.1 Local and global energy minima	358
		17.8.2 Molecular dynamics	358
		17.8.3 Stepwise bond rotation	359
		17.8.4 Monte Carlo and the Metropolis method	360
		17.8.5 Genetic and evolutionary algorithms	362
		17.9 Structure comparisons and overlays	363
		17.10 Identifying the active conformation	364
		17.10.1 X-ray crystallography	364
		17.10.2 Comparison of rigid and non-rigid ligands	365
		17.11 3D pharmacophore identification	366
		17.11.1 X-ray crystallography	367
		17.11.2 Structural comparison of active compounds	367
		17.11.3 Automatic identification of pharmacophores	367
		17.12 Docking procedures	368
		17.12.1 Manual docking	368
		17.12.2 Automatic docking	369
		17.12.3 Defining the molecular surface of a binding site	369
		17.12.4 Rigid docking by shape complementarity	370
		17.12.5 The use of grids in docking programs	372
		17.12.6 Rigid docking by matching hydrogen bonding groups	373
		17.12.7 Rigid docking of flexible ligands: the FLOG program	373
		17.12.8 Docking of flexible ligands: anchor and grow programs	373
		17.12.8.1 Directed Dock and Dock 4.0	374
		17.12.8.2 FlexX	374
		17.12.8.3 The Hammerhead program	376
		17.12.9 Docking of flexible ligands: simulated annealing and genetic algorithms	377
		17.13 Automated screening of databases for lead compounds and drug design	378
		17.14 Protein mapping	378
		17.14.1 Constructing a model protein: homology modelling	378
<b>PART D Tools of the trade</b>			
<b>16 Combinatorial and parallel synthesis</b>	<b>325</b>		
16.1 Combinatorial and parallel synthesis in medicinal chemistry projects	325		
16.2 Solid-phase techniques	326		
16.2.1 The solid support	326		
16.2.2 The anchor/linker	327		
16.2.3 Examples of solid-phase syntheses	329		
16.3 Planning and designing a compound library	330		
16.3.1 ‘Spider-like’ scaffolds	330		
16.3.2 Designing ‘drug-like’ molecules	330		
16.3.3 Synthesis of scaffolds	331		
16.3.4 Substituent variation	331		
16.3.5 Designing compound libraries for lead optimization	331		
16.3.6 Computer-designed libraries	332		
16.4 Testing for activity	333		
16.4.1 High-throughput screening	333		
16.4.2 Screening ‘on bead’ or ‘off bead’	333		
16.5 Parallel synthesis	334		
16.5.1 Solid-phase extraction	334		
16.5.2 The use of resins in solution-phase organic synthesis (SPOS)	336		
16.5.3 Reagents attached to solid support: catch and release	336		
16.5.4 Microwave technology	337		
16.5.5 Microfluidics in parallel synthesis	337		
16.6 Combinatorial synthesis	340		
16.6.1 The mix and split method in combinatorial synthesis	340		
16.6.2 Structure determination of the active compound(s)	341		
16.6.2.1 Tagging	341		
16.6.2.2 Photolithography	343		
16.6.3 Dynamic combinatorial synthesis	343		
Box 16.1 Examples of scaffolds	332		
Box 16.2 Dynamic combinatorial synthesis of vancomycin dimers	346		

17.14.2 Constructing a binding site: hypothetical pseudoreceptors	380	Box 18.3 Hansch equation for a series of antimalarial compounds	405
17.15 <i>De novo</i> drug design	381	<b>Case study 5: Design of a thymidylate synthase inhibitor</b>	<b>419</b>
17.15.1 General principles of <i>de novo</i> drug design	381		
17.15.2 Automated <i>de novo</i> drug design	383		
17.15.2.1 LUDI	383		
17.15.2.2 SPROUT	387		
17.15.2.3 LEGEND	389		
17.15.2.4 GROW, ALLEGROW, and SYNOPSIS	390		
17.16 Planning compound libraries	390		
17.17 Database handling	392		
Box 17.1 Energy minimizing apomorphine	352		
Box 17.2 Study of HOMO and LUMO orbitals	356		
Box 17.3 Finding conformations of cyclic structures by molecular dynamics	359		
Box 17.4 Identification of an active conformation	365		
Box 17.5 Constructing a receptor map	382		
Box 17.6 Designing a non-steroidal glucocorticoid agonist	391		
<b>18 Quantitative structure–activity relationships (QSAR)</b>	<b>395</b>		
18.1 Graphs and equations	395		
18.2 Physicochemical properties	396		
18.2.1 Hydrophobicity	397		
18.2.1.1 The partition coefficient ( <i>P</i> )	397		
18.2.1.2 The substituent hydrophobicity constant ( $\pi$ )	398		
18.2.1.3 <i>P</i> versus $\pi$	399		
18.2.2 Electronic effects	400		
18.2.3 Steric factors	402		
18.2.3.1 Taft's steric factor ( <i>E<sub>s</sub></i> )	403		
18.2.3.2 Molar refractivity	403		
18.2.3.3 Verloop steric parameter	403		
18.2.4 Other physicochemical parameters	404		
18.3 Hansch equation	404		
18.4 The Craig plot	404		
18.5 The Topliss scheme	406		
18.6 Bio-isosteres	409		
18.7 The Free–Wilson approach	409		
18.8 Planning a QSAR study	409		
18.9 Case study	410		
18.10 3D QSAR	413		
18.10.1 Defining steric and electrostatic fields	413		
18.10.2 Relating shape and electronic distribution to biological activity	414		
18.10.3 Advantages of CoMFA over traditional QSAR	415		
18.10.4 Potential problems of CoMFA	415		
18.10.5 Other 3D QSAR methods	416		
18.10.6 Case study: inhibitors of tubulin polymerization	416		
Box 18.1 Altering log <i>P</i> to remove central nervous system side effects	399		
Box 18.2 Insecticidal activity of diethyl phenyl phosphates	402		
		Box 18.3 Hansch equation for a series of antimalarial compounds	405
		<b>Case study 5: Design of a thymidylate synthase inhibitor</b>	<b>419</b>
		<b>PART E Selected topics in medicinal chemistry</b>	
		<b>19 Antibacterial agents</b>	<b>425</b>
		19.1 History of antibacterial agents	425
		19.2 The bacterial cell	427
		19.3 Mechanisms of antibacterial action	427
		19.4 Antibacterial agents which act against cell metabolism (antimetabolites)	428
		19.4.1 Sulphonamides	428
		19.4.1.1 The history of sulphonamides	428
		19.4.1.2 Structure–activity relationships	428
		19.4.1.3 Sulphanilamide analogues	428
		19.4.1.4 Applications of sulphonamides	429
		19.4.1.5 Mechanism of action	430
		19.4.2 Examples of other antimetabolites	432
		19.4.2.1 Trimethoprim	432
		19.4.2.2 Sulphones	432
		19.5 Antibacterial agents which inhibit cell wall synthesis	433
		19.5.1 Penicillins	433
		19.5.1.1 History of penicillins	433
		19.5.1.2 Structure of benzylpenicillin and phenoxymethylpenicillin	434
		19.5.1.3 Properties of benzylpenicillin	434
		19.5.1.4 Mechanism of action for penicillin	435
		19.5.1.5 Resistance to penicillin	438
		19.5.1.6 Methods of synthesizing penicillin analogues	440
		19.5.1.7 Structure–activity relationships of penicillins	441
		19.5.1.8 Penicillin analogues	441
		19.5.1.9 Synergism of penicillins with other drugs	447
		19.5.2 Cephalosporins	448
		19.5.2.1 Cephalosporin C	448
		19.5.2.2 Synthesis of cephalosporin analogues at position 7	449
		19.5.2.3 First-generation cephalosporins	450
		19.5.2.4 Second-generation cephalosporins	451
		19.5.2.5 Third-generation cephalosporins	452
		19.5.2.6 Fourth-generation cephalosporins	452
		19.5.2.7 Fifth-generation cephalosporins	453
		19.5.2.8 Resistance to cephalosporins	453
		19.5.3 Other $\beta$ -lactam antibiotics	454
		19.5.3.1 Carbapenems	454
		19.5.3.2 Monobactams	455
		19.5.4 $\beta$ -Lactamase inhibitors	455
		19.5.4.1 Clavulanic acid	455
		19.5.4.2 Penicillanic acid sulphone derivatives	457

## xx Detailed contents

19.5.4.3	Olivanic acids	457	Box 19.13	Clinical aspects of drugs acting on the plasma membrane	465
19.5.4.4	Avibactam	457	Box 19.14	Clinical aspects of aminoglycosides	468
19.5.5	Other drugs which act on bacterial cell wall biosynthesis	458	Box 19.15	Clinical aspects of tetracyclines and chloramphenicol	472
19.5.5.1	D-Cycloserine and bacitracin	458	Box 19.16	Clinical aspects of macrolides, lincosamides, streptogramins, oxazolidinones, and pleuromutilins	477
19.5.5.2	The glycopeptides: vancomycin and vancomycin analogues	459	Box 19.17	Synthesis of ciprofloxacin	479
19.6	Antibacterial agents which act on the plasma membrane structure	464	Box 19.18	Clinical aspects of quinolones and fluoroquinolones	480
19.6.1	Valinomycin and gramicidin A	464	Box 19.19	Clinical aspects of rifamycins and miscellaneous agents	482
19.6.2	Polymyxin B	464	Box 19.20	Organoarsenicals as antiparasitic drugs	487
19.6.3	Killer nanotubes	464			
19.6.4	Cyclic lipopeptides	464			
19.7	Antibacterial agents which impair protein synthesis: translation	466	<b>20</b>	<b>Antiviral agents</b>	<b>490</b>
19.7.1	Aminoglycosides	466	20.1	Viruses and viral diseases	490
19.7.2	Tetracyclines	468	20.2	Structure of viruses	490
19.7.3	Chloramphenicol	472	20.3	Life cycle of viruses	491
19.7.4	Macrolides	473	20.4	Vaccination	492
19.7.5	Lincosamides	474	20.5	Antiviral drugs: general principles	493
19.7.6	Streptogramins	475	20.6	Antiviral drugs used against DNA viruses	494
19.7.7	Oxazolidinones	475	20.6.1	Inhibitors of viral DNA polymerase	494
19.7.8	Pleuromutilins	476	20.6.2	Inhibitors of tubulin polymerization	498
19.8	Agents that act on nucleic acid transcription and replication	476	20.6.3	Antisense therapy	498
19.8.1	Quinolones and fluoroquinolones	476	20.7	Antiviral drugs acting against RNA viruses: the human immunodeficiency virus (HIV)	498
19.8.2	Aminoacridines	478	20.7.1	Structure and life cycle of HIV	498
19.8.3	Rifamycins	479	20.7.2	Antiviral therapy against HIV	500
19.8.4	Nitroimidazoles and nitrofurantoin	479	20.7.3	Inhibitors of viral reverse transcriptase	500
19.8.5	Inhibitors of bacterial RNA polymerase	479	20.7.3.1	Nucleoside reverse transcriptase inhibitors	500
19.9	Miscellaneous agents	480	20.7.3.2	Non-nucleoside reverse transcriptase inhibitors	501
19.10	Drug resistance	482	20.7.4	Protease inhibitors	504
19.10.1	Drug resistance by mutation	483	20.7.4.1	The HIV protease enzyme	504
19.10.2	Drug resistance by genetic transfer	483	20.7.4.2	Design of HIV protease inhibitors	505
19.10.3	Other factors affecting drug resistance	483	20.7.4.3	Saquinavir	507
19.10.4	The way ahead	484	20.7.4.4	Ritonavir and lopinavir	508
Box 19.1	Sulphonamide analogues with reduced toxicity	429	20.7.4.5	Indinavir	512
Box 19.2	Treatment of intestinal infections	430	20.7.4.6	Nelfinavir	513
Box 19.3	Clinical properties of benzylpenicillin and phenoxymethylpenicillin	435	20.7.4.7	Palinavir	514
Box 19.4	<i>Pseudomonas aeruginosa</i>	438	20.7.4.8	Amprenavir and darunavir	514
Box 19.5	The isoxazolyl penicillins	444	20.7.4.9	Atazanavir	514
Box 19.6	Clinical aspects of $\beta$ -lactamase-resistant penicillins	444	20.7.4.10	Tipranavir	515
Box 19.7	Ampicillin prodrugs	446	20.7.4.11	Alternative design strategies for antiviral drugs targeting the HIV protease enzyme	516
Box 19.8	Clinical aspects of broad-spectrum penicillins	447	20.7.5	Inhibitors of other targets	517
Box 19.9	Synthesis of 3-methylated cephalosporins	451	20.8	Antiviral drugs acting against RNA viruses: flu virus	519
Box 19.10	Clinical aspects of cephalosporins	454	20.8.1	Structure and life cycle of the influenza virus	519
Box 19.11	Clinical aspects of miscellaneous $\beta$ -lactam antibiotics	456	20.8.2	Ion channel disrupters: adamantanes	521
Box 19.12	Clinical aspects of cycloserine, bacitracin, and vancomycin	464			



20.8.3	Neuraminidase inhibitors	522	21.1.4	Abnormal signalling pathways	544
20.8.3.1	Structure and mechanism of neuraminidase	522	21.1.5	Insensitivity to growth-inhibitory signals	545
20.8.3.2	Transition-state inhibitors: development of zanamivir (Relenza)	524	21.1.6	Abnormalities in cell cycle regulation	545
20.8.3.3	Transition-state inhibitors: 6-carboxamides	525	21.1.7	Apoptosis and the p53 protein	547
20.8.3.4	Carbocyclic analogues: development of oseltamivir (Tamiflu)	526	21.1.8	Telomeres	548
20.8.3.5	Other ring systems	528	21.1.9	Angiogenesis	549
20.8.3.6	Resistance studies	529	21.1.10	Tissue invasion and metastasis	550
20.9	Antiviral drugs acting against RNA viruses: cold virus	530	21.1.11	Treatment of cancer	550
20.10	Antiviral drugs acting against RNA viruses: hepatitis C	531	21.1.12	Resistance	552
20.10.1	Inhibitors of HCV NS3-4A protease	532	21.2	Drugs acting directly on nucleic acids	553
20.10.1.1	Introduction	532	21.2.1	Intercalating agents	553
20.10.1.2	Design of boceprevir and telaprevir	532	21.2.2	Non-intercalating agents which inhibit the action of topoisomerase enzymes on DNA	555
20.10.1.3	Second-generation protease inhibitors	534	21.2.2.1	Podophyllotoxins	555
20.10.2	Inhibitors of HCV NS5B RNA-dependent RNA polymerase	535	21.2.2.2	Camptothecins	555
20.10.3	Inhibitors of HCV NS5A protein	535	21.2.3	Alkylating and metallating agents	555
20.10.4	Other targets	538	21.2.3.1	Nitrogen mustards	556
20.11	Broad-spectrum antiviral agents	539	21.2.3.2	Cisplatin and cisplatin analogues: metallating agents	558
20.11.1	Agents acting against cytidine triphosphate synthetase	539	21.2.3.3	CC 1065 analogues	558
20.11.2	Agents acting against S-adenosylhomocysteine hydrolase	539	21.2.3.4	Other alkylating agents	558
20.11.3	Ribavirin	540	21.2.4	Chain cutters	559
20.11.4	Interferons	540	21.2.5	Antisense therapy	559
20.11.5	Antibodies and ribozymes	540	21.3	Drugs acting on enzymes: antimetabolites	560
20.12	Bioterrorism and smallpox	541	21.3.1	Dihydrofolate reductase inhibitors	560
Box 20.1	Clinical aspects of viral DNA polymerase inhibitors	497	21.3.2	Inhibitors of thymidylate synthase	561
Box 20.2	Clinical aspects of antiviral drugs used against HIV	501	21.3.3	Inhibitors of ribonucleotide reductase	563
Box 20.3	Clinical aspects of reverse transcriptase inhibitors	503	21.3.4	Inhibitors of adenosine deaminase	564
Box 20.4	Clinical aspects of protease inhibitors	516	21.3.5	Inhibitors of DNA polymerases	564
Box 20.5	Clinical aspects of antiviral agents used in the treatment of hepatitis C	538	21.3.6	Purine antagonists	565
<b>21</b>	<b>Anticancer agents</b>	<b>543</b>	21.4	Hormone-based therapies	567
21.1	Cancer: an introduction	543	21.4.1	Glucocorticoids, estrogens, progestins, and androgens	567
21.1.1	Definitions	543	21.4.2	Luteinizing hormone-releasing hormone receptor agonists and antagonists	568
21.1.2	Causes of cancer	543	21.4.3	Anti-estrogens	568
21.1.3	Genetic faults leading to cancer: proto-oncogenes and oncogenes	543	21.4.4	Anti-androgens	568
21.1.3.1	Activation of proto-oncogenes	543	21.4.5	Aromatase inhibitors	570
21.1.3.2	Inactivation of tumour suppression genes (anti-oncogenes)	544	21.5	Drugs acting on structural proteins	572
21.1.3.3	The consequences of genetic defects	544	21.5.1	Agents which inhibit tubulin polymerization	572
			21.5.2	Agents which inhibit tubulin depolymerization	573
			21.6	Inhibitors of signalling pathways	575
			21.6.1	Inhibition of farnesyl transferase and the Ras protein	575
			21.6.2	Protein kinase inhibitors	577
			21.6.2.1	Kinase inhibitors of the epidermal growth factor receptor (EGFR)	579
			21.6.2.2	Kinase inhibitors of Abelson tyrosine kinase, c-KIT, PDGFR, and SRC	582
			21.6.2.3	Inhibitors of cyclin-dependent kinases (CDKs)	586
			21.6.2.4	Kinase inhibitors of the MAPK signal transduction pathway	587
			21.6.2.5	Kinase inhibitors of PI3K-PIP <sub>3</sub> pathways	588

21.6.2.6 Kinase inhibitors of anaplastic lymphoma kinase (ALK)	589	Box 21.11 Clinical aspects of antibodies and antibody–drug conjugates	609
21.6.2.7 Kinase inhibitors of RET and KIF5B-RET	590	Box 21.12 Gemtuzumab ozogamicin: an antibody–drug conjugate	613
21.6.2.8 Kinase inhibitors of Janus kinase	590		
21.6.2.9 Kinase inhibitors of vascular endothelial growth factor receptor (VEGFR)	591	<b>22 Cholinergics, anticholinergics, and anticholinesterases</b>	<b>620</b>
21.6.2.10 Multi-receptor tyrosine kinase inhibitors	591	22.1 The peripheral nervous system	620
21.6.2.11 Kinase inhibition involving protein–protein binding interactions	595	22.2 Motor nerves of the peripheral nervous system	620
21.6.3 Receptor antagonists of the hedgehog signalling pathway	595	22.2.1 The somatic motor nervous system	621
21.7 Miscellaneous enzyme inhibitors	596	22.2.2 The autonomic motor nervous system	621
21.7.1 Matrix metalloproteinase inhibitors	596	22.2.3 The enteric system	622
21.7.2 Proteasome inhibitors	597	22.2.4 Defects in motor nerve transmission	622
21.7.3 Histone deacetylase inhibitors	600	22.3 The cholinergic system	622
21.7.4 Inhibitors of poly ADP ribose polymerase	602	22.3.1 The cholinergic signalling system	622
21.7.5 Other enzyme targets	603	22.3.2 Presynaptic control systems	623
21.8 Agents affecting apoptosis	603	22.3.3 Cotransmitters	623
21.9 Miscellaneous anticancer agents	604	22.4 Agonists at the cholinergic receptor	623
21.9.1 Synthetic agents	605	22.5 Acetylcholine: structure, SAR, and receptor binding	624
21.9.2 Natural products	606	22.6 The instability of acetylcholine	626
21.9.3 Protein therapy	608	22.7 Design of acetylcholine analogues	627
21.9.4 Modulation of transcription factor–coactivator interactions	608	22.7.1 Steric shields	627
21.10 Antibodies, antibody conjugates, and gene therapy	609	22.7.2 Electronic effects	627
21.10.1 Monoclonal antibodies	609	22.7.3 Combining steric and electronic effects	628
21.10.2 Antibody–drug conjugates	611	22.8 Clinical uses for cholinergic agonists	628
21.10.3 Antibody-directed enzyme prodrug therapy (ADEPT)	612	22.8.1 Muscarinic agonists	628
21.10.4 Antibody-directed abzyme prodrug therapy (ADAPT)	614	22.8.2 Nicotinic agonists	628
21.10.5 Gene-directed enzyme prodrug therapy (GDEPT)	614	22.9 Antagonists of the muscarinic cholinergic receptor	629
21.10.6 Other forms of gene therapy	615	22.9.1 Actions and uses of muscarinic antagonists	629
21.11 Photodynamic therapy	615	22.9.2 Muscarinic antagonists	629
21.12 Viral therapy	616	22.9.2.1 Atropine and hyoscyne	629
Box 21.1 Clinical aspects of intercalating agents	554	22.9.2.2 Structural analogues of atropine and hyoscyne	631
Box 21.2 Clinical aspects of non-intercalating agents inhibiting the action of topoisomerase enzymes on DNA	556	22.9.2.3 Simplified analogues of atropine	631
Box 21.3 Clinical aspects of alkylating and metallating agents	559	22.9.2.4 Quinuclidine muscarinic agents	633
Box 21.4 Clinical aspects of antimetabolites	565	22.9.2.5 Other muscarinic antagonists	633
Box 21.5 Clinical aspects of hormone-based therapies	571	22.10 Antagonists of the nicotinic cholinergic receptor	635
Box 21.6 Clinical aspects of drugs acting on structural proteins	575	22.10.1 Applications of nicotinic antagonists	635
Box 21.7 General synthesis of gefitinib and related analogues	582	22.10.2 Nicotinic antagonists	635
Box 21.8 General synthesis of imatinib and analogues	586	22.10.2.1 Curare and tubocurarine	635
Box 21.9 Design of sorafenib	592	22.10.2.2 Decamethonium and suxamethonium	636
Box 21.10 Clinical aspects of kinase inhibitors	593	22.10.2.3 Steroidal neuromuscular blocking agents	637
		22.10.2.4 Atracurium and mivacurium	637
		22.10.2.5 Other nicotinic antagonists	638
		22.11 Receptor structures	639
		22.12 Anticholinesterases and acetylcholinesterase	640
		22.12.1 Effect of anticholinesterases	640
		22.12.2 Structure of the acetylcholinesterase enzyme	640
		22.12.3 The active site of acetylcholinesterase	640
		22.12.3.1 Crucial amino acids within the active site	641
		22.12.3.2 Mechanism of hydrolysis	641

22.13 Anticholinesterase drugs	642	23.11.3.3 Selective $\beta_1$ -blockers (second-generation $\beta$ -blockers)	669
22.13.1 Carbamates	642	23.11.3.4 Short-acting $\beta$ -blockers	669
22.13.1.1 Physostigmine	642	23.12 Other drugs affecting adrenergic transmission	672
22.13.1.2 Analogues of physostigmine	644	23.12.1 Drugs that affect the biosynthesis of adrenergics	672
22.13.2 Organophosphorus compounds	645	23.12.2 Drugs inhibiting the uptake of noradrenaline into storage vesicles	672
22.13.2.1 Nerve agents	645	23.12.3 Release of noradrenaline from storage vesicles	673
22.13.2.2 Medicines	646	23.12.4 Reuptake inhibitors of noradrenaline into presynaptic neurons	673
22.13.2.3 Insecticides	646	23.12.5 Inhibition of metabolic enzymes	675
22.14 Pralidoxime: an organophosphate antidote	647	Box 23.1 Clinical aspects of adrenergic agents	656
22.15 Anticholinesterases as 'smart drugs'	648	Box 23.2 Synthesis of salbutamol	664
22.15.1 Acetylcholinesterase inhibitors	648	Box 23.3 Synthesis of aryloxypropanolamines	668
22.15.2 Dual-action agents acting on the acetylcholinesterase enzyme	649	Box 23.4 Clinical aspects of $\beta$ -blockers	670
22.15.3 Multi-targeted agents acting on the acetylcholinesterase enzyme and the muscarinic $M_2$ receptor	650		
Box 22.1 Clinical applications for muscarinic antagonists	634		
Box 22.2 Muscarinic antagonists for the treatment of COPD	634		
Box 22.3 Mosses play it smart	652		
<b>23 Drugs acting on the adrenergic nervous system</b>	<b>654</b>	<b>24 The opioid analgesics</b>	<b>678</b>
23.1 The adrenergic nervous system	654	24.1 History of opium	678
23.1.1 Peripheral nervous system	654	24.2 The active principle: morphine	678
23.1.2 Central nervous system	654	24.2.1 Isolation of morphine	678
23.2 Adrenergic receptors	654	24.2.2 Structure and properties	679
23.2.1 Types of adrenergic receptor	654	24.3 Structure–activity relationships	679
23.2.2 Distribution of receptors	655	24.4 The molecular target for morphine: opioid receptors	682
23.3 Endogenous agonists for the adrenergic receptors	656	24.5 Morphine: pharmacodynamics and pharmacokinetics	682
23.4 Biosynthesis of catecholamines	656	24.6 Morphine analogues	684
23.5 Metabolism of catecholamines	657	24.6.1 Variation of substituents	684
23.6 Neurotransmission	657	24.6.2 Drug extension	684
23.6.1 The neurotransmission process	657	24.6.3 Simplification or drug dissection	686
23.6.2 Cotransmitters	657	24.6.3.1 Removing ring E	686
23.6.3 Presynaptic receptors and control	658	24.6.3.2 Removing ring D	686
23.7 Drug targets	659	24.6.3.3 Removing rings C and D	687
23.8 The adrenergic binding site	659	24.6.3.4 Removing rings B, C, and D	688
23.9 Structure–activity relationships	660	24.6.3.5 Removing rings B, C, D, and E	689
23.9.1 Important binding groups on catecholamines	660	24.6.4 Rigidification	690
23.9.2 Selectivity for $\alpha$ - versus $\beta$ -adrenoceptors	661	24.7 Agonists and antagonists	693
23.10 Adrenergic agonists	662	24.8 Endogenous opioid peptides and opioids	695
23.10.1 General adrenergic agonists	662	24.8.1 Endogenous opioid peptides	695
23.10.2 $\alpha_1$ -, $\alpha_2$ -, $\beta_1$ -, and $\beta_3$ -Agonists	662	24.8.2 Analogues of enkephalins and $\delta$ -selective opioids	696
23.10.3 $\beta_2$ -Agonists and the treatment of asthma	663	24.8.3 Binding theories for enkephalins	697
23.11 Adrenergic receptor antagonists	666	24.8.4 Inhibitors of peptidases	699
23.11.1 General $\alpha/\beta$ -blockers	666	24.8.5 Endogenous morphine	699
23.11.2 $\alpha$ -Blockers	666	24.9 The future	700
23.11.3 $\beta$ -Blockers as cardiovascular drugs	667	24.9.1 The message-address concept	700
23.11.3.1 First-generation $\beta$ -blockers	667	24.9.2 Receptor dimers	700
23.11.3.2 Structure–activity relationships of aryloxypropanolamines	668	24.9.3 Selective opioid agonists versus multi-targeted opioids	701
		24.9.4 Peripheral-acting opioids	701
		24.10 Case study: design of nalfurafine	701
		Box 24.1 Clinical aspects of morphine	679
		Box 24.2 Synthesis of <i>N</i> -alkylated morphine analogues	685



Box 24.3 Opioids as antidiarrhoeal agents	690	<b>26 Cardiovascular drugs</b>	<b>735</b>
Box 24.4 Synthesis of the orvinols	692	26.1 Introduction	735
Box 24.5 A comparison of opioids and their effects on opioid receptors	695	26.2 The cardiovascular system	735
Box 24.6 Design of naltrindole	698	26.3 Antihypertensives affecting the activity of the RAAS system	737
<b>25 Anti-ulcer agents</b>	<b>705</b>	26.3.1 Introduction	737
25.1 Peptic ulcers	705	26.3.2 Renin inhibitors	737
25.1.1 Definition	705	26.3.3 ACE inhibitors	738
25.1.2 Causes	705	26.3.4 Angiotensin receptor antagonists	739
25.1.3 Treatment	705	26.3.5 Mineralocorticoid receptor antagonists	741
25.1.4 Gastric acid release	705	26.3.6 Dual-action agents	742
25.2 H <sub>2</sub> antagonists	706	26.4 Endothelin receptor antagonists as antihypertensive agents	742
25.2.1 Histamine and histamine receptors	707	26.4.1 Endothelins and endothelin receptors	742
25.2.2 Searching for a lead	708	26.4.2 Endothelin antagonists	742
25.2.2.1 Histamine	708	26.4.3 Dual-action agents	743
25.2.2.2 N <sup>α</sup> -Guanylhistamine	708	26.5 Vasodilators	744
25.2.3 Developing the lead: a chelation bonding theory	711	26.5.1 Modulators of soluble guanylate cyclase	744
25.2.4 From partial agonist to antagonist: the development of burimamide	711	26.5.2 Phosphodiesterase type 5 inhibitors	746
25.2.5 Development of metiamide	713	26.5.3 Nephilysin inhibitors	747
25.2.6 Development of cimetidine	716	26.5.4 Prostacyclin agonists	747
25.2.7 Cimetidine	717	26.5.5 Miscellaneous vasodilators	747
25.2.7.1 Biological activity	717	26.6 Calcium entry blockers	748
25.2.7.2 Structure and activity	718	26.6.1 Introduction	748
25.2.7.3 Metabolism	718	26.6.2 Dihydropyridines	750
25.2.8 Further studies of cimetidine analogues	719	26.6.3 Phenylalkylamines	751
25.2.8.1 Conformational isomers	719	26.6.4 Benzothiazepines	752
25.2.8.2 Desolvation	720	26.7 Funny ion channel inhibitors	753
25.2.8.3 Development of the nitroketeneaminal binding group	720	26.8 Lipid-regulating agents	754
25.2.9 Further H <sub>2</sub> antagonists	722	26.8.1 Statins	754
25.2.9.1 Ranitidine	722	26.8.2 Fibrates	754
25.2.9.2 Famotidine and nizatidine	723	26.8.3 Dual- and pan-PPAR agonists	755
25.2.9.3 H <sub>2</sub> antagonists with prolonged activity	724	26.8.4 Antisense drugs	756
25.2.10 Comparison of H <sub>1</sub> and H <sub>2</sub> antagonists	724	26.8.5 Inhibitors of transfer proteins	756
25.2.11 H <sub>2</sub> receptors and H <sub>2</sub> antagonists	725	26.8.6 Antibodies as lipid-lowering agents	756
25.3 Proton pump inhibitors	725	26.9 Antithrombotic agents	757
25.3.1 Parietal cells and the proton pump	725	26.9.1 Anticoagulants	758
25.3.2 Proton pump inhibitors	726	26.9.1.1 Introduction	758
25.3.3 Mechanism of inhibition	727	26.9.1.2 Direct thrombin inhibitors	758
25.3.4 Metabolism of proton pump inhibitors	728	26.9.1.3 Factor Xa inhibitors	759
25.3.5 Design of omeprazole and esomeprazole	728	26.9.2 Antiplatelet agents	760
25.3.6 Other proton pump inhibitors	731	26.9.2.1 Introduction	760
25.4 <i>Helicobacter pylori</i> and the use of antibacterial agents	732	26.9.2.2 PAR-1 antagonists	760
25.4.1 Discovery of <i>Helicobacter pylori</i>	732	26.9.2.3 P2Y <sub>12</sub> antagonists	761
25.4.2 Treatment	732	26.9.2.4 GpIIb/IIIa antagonists	763
25.5 Traditional and herbal medicines	733	26.9.3 Fibrinolytic drugs	763
Box 25.1 Synthesis of cimetidine	718	Box 26.1 Synthesis of dihydropyridines	749
Box 25.2 Synthesis of omeprazole and esomeprazole	731	<b>Case study 6: Steroidal anti-inflammatory agents</b>	<b>766</b>
		■ CS6.1 Introduction to steroids	766
		■ CS6.2 Orally active analogues of cortisol	767
		■ CS6.3 Topical glucocorticoids as anti-inflammatory agents	768

<b>Case study 7: Current research into antidepressant agents</b>	<b>776</b>	<b>■ CS9.6 The development of rivoraxaban</b>	<b>793</b>
■ CS7.1 Introduction	776	■ CS9.7 The development of edoxaban	794
■ CS7.2 The monoamine hypothesis	776	<b>Case study 10: Reversible inhibitors of HCV NS3-4A protease</b>	<b>795</b>
■ CS7.3 Current antidepressant agents	776	■ CS10.1 Introduction	795
■ CS7.4 Current areas of research	777	■ CS10.2 Identification of a lead compound	795
■ CS7.5 Antagonists for the 5-HT <sub>7</sub> receptor	777	■ CS10.3 Modifications of the lead compound	796
<b>Case study 8: The design and development of aliskiren</b>	<b>781</b>	■ CS10.4 From hexapeptide to tripeptide	797
■ CS8.1 Introduction	781	■ CS10.5 From tripeptide to macrocycle (BILN-2061)	798
■ CS8.2 Reaction catalysed by renin	781	■ CS10.6 From BILN-2061 to simeprevir	799
■ CS8.3 From lead compound to peptide inhibitors	781	Appendix 1 Essential amino acids	801
■ CS8.4 Peptidomimetic strategies	783	Appendix 2 The standard genetic code	802
■ CS8.5 Design of non-peptide inhibitors	783	Appendix 3 Statistical data for QSAR	803
■ CS8.6 Optimization of the structure	785	Appendix 4 The action of nerves	807
<b>Case study 9: Factor Xa inhibitors</b>	<b>788</b>	Appendix 5 Microorganisms	811
■ CS9.1 Introduction	788	Appendix 6 Trade names and drugs	813
■ CS9.2 The target	788	Appendix 7 Hydrogen bonding interactions	822
■ CS9.3 General strategies in the design of factor Xa inhibitors	789	Glossary	824
■ CS9.4 Apixaban: from hit structure to lead compound	789	General further reading	845
■ CS9.5 Apixaban: from lead compound to final structure	790	Index	847

# List of boxes

## General interest

3.1	The external control of enzymes by nitric oxide	39
7.1	A cure for antifreeze poisoning	94
7.2	Irreversible inhibition for the treatment of obesity	96
7.3	Suicide substrates	100
7.4	Designing drugs to be isozyme selective	101
7.5	Action of toxins on enzymes	102
7.6	Kinase inhibitors	104
8.1	An unexpected agonist	113
8.2	Estradiol and the estrogen receptor	116
10.1	Antidepressant drugs acting on transport proteins	145
10.2	Targeting transcription factor–coactivator interactions	149
10.3	Cyclodextrins as drug scavengers	159
11.1	Metabolism of an antiviral agent	175
12.1	Recently discovered targets: the caspases	198
12.2	Pitfalls in choosing particular targets	200
12.3	Early tests for potential toxicity	201
12.4	Selective optimization of side activities (SOSA)	213
12.5	Natural ligands as lead compounds	214
12.6	Examples of serendipity	216
12.7	The use of NMR spectroscopy in finding lead compounds	217
12.8	Click chemistry <i>in situ</i>	219
13.1	Converting an enzyme substrate to an inhibitor by extension tactics	240
13.2	Simplification	245
13.3	Rigidification tactics in drug design	249
13.4	The structure-based drug design of crizotinib	251
14.1	The use of bio-isosteres to increase absorption	259
14.2	Shortening the lifetime of a drug	264
14.3	Identifying and replacing potentially toxic groups	267
14.4	Varying esters in prodrugs	269
14.5	Prodrugs masking toxicity and side effects	271
14.6	Prodrugs to improve water solubility	272
15.1	Drug metabolism studies and drug design	286
16.1	Examples of scaffolds	332

17.1	Energy minimizing apomorphine	352
17.2	Study of HOMO and LUMO orbitals	356
17.3	Finding conformations of cyclic structures by molecular dynamics	359
17.4	Identification of an active conformation	365
17.5	Constructing a receptor map	382
17.6	Designing a non-steroidal glucocorticoid agonist	391
18.1	Altering log <i>P</i> to remove central nervous system side effects	399
18.2	Insecticidal activity of diethyl phenyl phosphates	402
18.3	Hansch equation for a series of antimalarial compounds	405
19.1	Sulphonamide analogues with reduced toxicity	429
19.2	Treatment of intestinal infections	430
19.5	The isoxazolyl penicillins	444
19.7	Ampicillin prodrugs	446
19.20	Organoarsenicals as antiparasitic drugs	487
21.9	Design of sorafenib	592
21.12	Gemtuzumab ozogamicin: an antibody–drug conjugate	613
22.3	Mosses play it smart	652
24.3	Opioids as antidiarrhoeal agents	690
24.6	Design of naltrindole	698

## Synthesis

15.2	Synthesis of ebalzotan	296
15.3	Synthesis of ICI D7114	297
16.2	Dynamic combinatorial synthesis of vancomycin dimers	346
19.9	Synthesis of 3-methylated cephalosporins	451
19.17	Synthesis of ciprofloxacin	479
21.7	General synthesis of gefitinib and related analogues	582
21.8	General synthesis of imatinib and analogues	586
23.2	Synthesis of salbutamol	664
23.3	Synthesis of aryloxypropanolamines	668
24.2	Synthesis of <i>N</i> -alkylated morphine analogues	685
24.4	Synthesis of the orvinols	692
25.1	Synthesis of cimetidine	718
25.2	Synthesis of omeprazole and esomeprazole	731

26.1	Synthesis of dihydropyridines	749	20.2	Clinical aspects of antiviral drugs used against HIV	501
CS2.1	Synthesis of captopril and enalaprilat	307	20.3	Clinical aspects of reverse transcriptase inhibitors	503
CS4.1	Synthesis of oxamniquine	320	20.4	Clinical aspects of protease inhibitors	516
<div style="background-color: #e6f2ff; padding: 5px;"><b>Clinical correlation</b></div>					
19.3	Clinical properties of benzylpenicillin and phenoxymethylpenicillin	435	20.5	Clinical aspects of antiviral agents used in the treatment of hepatitis C	538
19.4	<i>Pseudomonas aeruginosa</i>	438	21.1	Clinical aspects of intercalating agents	554
19.6	Clinical aspects of $\beta$ -lactamase-resistant penicillins	444	21.2	Clinical aspects of non-intercalating agents inhibiting the action of topoisomerase enzymes on DNA	556
19.8	Clinical aspects of broad-spectrum penicillins	447	21.3	Clinical aspects of alkylating and metallating agents	559
19.10	Clinical aspects of cephalosporins	454	21.4	Clinical aspects of antimetabolites	565
19.11	Clinical aspects of miscellaneous $\beta$ -lactam antibiotics	456	21.5	Clinical aspects of hormone-based therapies	571
19.12	Clinical aspects of cycloserine, bacitracin, and vancomycin	464	21.6	Clinical aspects of drugs acting on structural proteins	575
19.13	Clinical aspects of drugs acting on the plasma membrane	465	21.10	Clinical aspects of kinase inhibitors	593
19.14	Clinical aspects of aminoglycosides	468	21.11	Clinical aspects of antibodies and antibody–drug conjugates	609
19.15	Clinical aspects of tetracyclines and chloramphenicol	472	22.1	Clinical applications for muscarinic antagonists	634
19.16	Clinical aspects of macrolides, lincosamides, streptogramins, oxazolidinones, and pleuromutilins	477	22.2	Muscarinic antagonists for the treatment of COPD	634
19.18	Clinical aspects of quinolones and fluoroquinolones	480	23.1	Clinical aspects of adrenergic agents	656
19.19	Clinical aspects of rifamycins and miscellaneous agents	482	23.4	Clinical aspects of $\beta$ -blockers	670
20.1	Clinical aspects of viral DNA polymerase inhibitors	497	24.1	Clinical aspects of morphine	679
			24.5	A comparison of opioids and their effects on opioid receptors	695
			CS3.1	Clinical properties of artemisinin and analogues	313
			CS6.1	Clinical aspects of glucocorticoids	774

# Acronyms and abbreviations

Note: Abbreviations for amino acids are given in Appendix 1

5-HT5	hydroxytryptamine (serotonin)	CNS	central nervous system
7-ACA7	aminocephalosporinic acid	CoA	coenzyme A
6-APA6	aminopenicillanic acid	CoMFA	comparative molecular field analysis
ACE	angiotensin-converting enzyme	COMT	catechol <i>O</i> -methyltransferase
ACh	acetylcholine	COPD	chronic obstructive pulmonary disease
AChE	acetylcholinesterase	COX	cyclooxygenase
ACP	acyl carrier protein	CSD	Cambridge Structural Database
ACT	artemisinin combination therapy	CYP	enzymes that constitute the cytochrome P450 family
ADAPT	antibody-directed abzyme prodrug therapy		
ADEPT	antibody-directed enzyme prodrug therapy	D-	
ADH	alcohol dehydrogenase	receptor	dopamine receptor
ADME	absorption, distribution, metabolism, excretion	dATP	deoxyadenosine triphosphate
ADP	adenosine 5'-diphosphate	DCC	dicyclohexylcarbodiimide
AGO	argonaute protein	dCTP	deoxycytosine triphosphate
AIC	5-aminoimidazole-4-carboxamide	DG	diacylglycerol
AIDS	acquired immune deficiency syndrome	dGTP	deoxyguanosine triphosphate
Akt	protein kinase B	DHFR	dihydrofolate reductase
ALK	anaplastic lymphoma kinase	Dhh	desert hedgehog
AME	aminoglycoside modifying enzyme	DMAP	dimethylaminopyridine
AML	acute myeloid leukaemia	DNA	deoxyribonucleic acid
AMP	adenosine 5'-monophosphate	DOR	delta opioid receptor
AT	angiotensin	dsDNA	double-stranded DNA
ATP	adenosine 5'-triphosphate	dsRNA	double-stranded RNA
AUC	area under the curve	dTMP	deoxythymidylate monophosphate
BiTE	bi-specific T-cell engager	dTTP	deoxythymidylate triphosphate
BuChE	butyrylcholinesterase	dUMP	deoxyuridylate monophosphate
BTK	Bruton's tyrosine kinase	EC <sub>50</sub>	concentration of drug required to produce 50% of the maximum possible effect
cAMP	cyclic AMP	E <sub>s</sub>	Taft's steric factor
β-CCE	carboline-3-carboxylate	EGF	epidermal growth factor
CCK	cholecystokinin	EGFR	epidermal growth factor receptor
CDKs	cyclin-dependent kinases	EMA	European Agency for the Evaluation of Medicinal Products
CETP	cholesteryl ester transfer protein	EPC	European Patent Convention
cGMP	cyclic GMP	EPO	European Patent Office
CHO cells	Chinese hamster ovarian cells	EPO	erythropoietin
CKIs	cyclin-dependent kinase inhibitors	ErbB	epidermal growth factor receptor
c-KIT	mast/stem cell growth factor receptor	ERK	see MAPK
Clog <i>P</i>	calculated logarithm of the partition coefficient	ET	endothelin
c-MET		FDA	US Food and Drug Administration
receptor	hepatocyte growth factor receptor	FdUMP	fluorodeoxyuracil monophosphate
CML	chronic myeloid leukaemia	FGF	fibroblast growth factor
CMV	cytomegalovirus	FGFR	fibroblast growth factor receptor

<b>FH<sub>4</sub></b>	tetrahydrofolate	<b>HMG-SCoA</b>	3-hydroxy-3-methylglutaryl-coenzyme A
<b>F</b>	oral bioavailability	<b>HMGR</b>	3-hydroxy-3-methylglutaryl-coenzyme A reductase
<b>F</b>	inductive effect of an aromatic substituent in QSAR	<b>HOMO</b>	highest occupied molecular orbital
<b>F-SPE</b>	fluorous solid-phase extraction	<b>HPLC</b>	high-performance liquid chromatography
<b>FLOG</b>	Flexible Ligands Orientated on Grid	<b>HPMA</b>	<i>N</i> -(2-hydroxypropyl)methacrylamide
<b>FPGS</b>	folylpolyglutamate synthetase	<b>HPT</b>	human intestinal di-/tripeptide transporter
<b>FPP</b>	farnesyl diphosphate	<b>HRV</b>	human rhinoviruses
<b>FT</b>	farnesyl transferase	<b>HSV</b>	herpes simplex virus
<b>FTI</b>	farnesyl transferase inhibitor	<b>HTS</b>	high-throughput screening
<b>G-</b>		<b>IC<sub>50</sub></b>	concentration of drug required to inhibit a target by 50%
<b>protein</b>	guanine nucleotide binding protein	<b>ICMT1</b>	isoprenylcysteine carboxylmethyltransferase
<b>GABA</b>	$\gamma$ -aminobutyric acid	<b>If</b>	funny ion channels
<b>GAP</b>	GTPase activating protein	<b>IGF-1R</b>	insulin growth factor 1 receptor
<b>GCP</b>	Good Clinical Practice	<b>Ihh</b>	Indian hedgehog
<b>GDEPT</b>	gene-directed enzyme prodrug therapy	<b>IND</b>	Investigational exemption to a New Drug application
<b>GDP</b>	guanosine diphosphate	<b>IP<sub>3</sub></b>	inositol triphosphate
<b>GEF</b>	guanine nucleotide exchange factors	<b>IPER</b>	International Preliminary Examination Report
<b>GGTase</b>	geranylgeranyltransferase	<b>IRB</b>	Institutional Review Board
<b>GH</b>	growth hormone	<b>ISR</b>	International Search Report
<b>GIT</b>	gastrointestinal tract	<b>ITC</b>	isothermal titration calorimetry
<b>GLP</b>	Good Laboratory Practice	<b>IUPAC</b>	International Union of Pure and Applied Chemistry
<b>GMC</b>	General Medical Council	<b>IV</b>	intravenous
<b>GMP</b>	Good Manufacturing Practice	<b>JAK</b>	Janus kinase
<b>GMP</b>	guanosine monophosphate	<b>K<sub>D</sub></b>	dissociation binding constant
<b>GnRH</b>	gonadotrophin-releasing hormone	<b>K<sub>i</sub></b>	inhibition constant
<b>gp</b>	glycoprotein	<b>K<sub>M</sub></b>	Michaelis constant
<b>GRB2</b>	growth factor receptor bound protein 2	<b>KOR</b>	kappa opioid receptor
<b>gt</b>	genotype	<b>LAAM</b>	L- $\alpha$ -acetylmethadol
<b>GTP</b>	guanosine triphosphate	<b>LD<sub>50</sub></b>	lethal dose required to kill 50% of a test sample of animals
<b>h-PEPT</b>	human intestinal proton-dependent oligopeptide transporter	<b>LDH</b>	lactate dehydrogenase
<b>H-</b>		<b>LDL</b>	low density lipoprotein
<b>receptor</b>	histamine receptor	<b>LH</b>	luteinizing hormone
<b>HA</b>	haemagglutinin	<b>LHRH</b>	luteinizing hormone-releasing hormones
<b>HAART</b>	highly active antiretroviral therapy	<b>LipE</b>	lipophilic efficiency
<b>HAMA</b>	human anti-mouse antibodies	<b>log P</b>	logarithm of the partition coefficient
<b>HBA</b>	hydrogen bond acceptor	<b>LDL</b>	low density lipoprotein
<b>HBD</b>	hydrogen bond donor	<b>LUMO</b>	lowest unoccupied molecular orbital
<b>HCV</b>	hepatitis C virus	<b>M-</b>	
<b>HDL</b>	high density lipoprotein	<b>receptor</b>	muscarinic receptor
<b>HERG</b>	human ether-a-go-go related gene	<b>MAA</b>	Marketing Authorization Application
<b>HER</b>	human epidermal growth factor receptor		
<b>HGFR</b>	hepatocyte growth factor receptor		
<b>HIF</b>	hypoxia-inducible factor		
<b>HIV</b>	human immunodeficiency virus		

<b>MAB</b>	monoclonal antibody	<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitor
<b>MAO</b>	monoamine oxidase	<b>NO</b>	nitric oxide
<b>MAOI</b>	monoamine oxidase inhibitor	<b>NOR</b>	nociceptin opioid receptor
<b>MAOS</b>	microwave assisted organic synthesis	<b>NOS</b>	nitric oxide synthase
<b>MAP</b>	mitogen-activated protein	<b>NRTI</b>	nucleoside reverse transcriptase inhibitor
<b>MAPK</b>	mitogen-activated protein kinases	<b>NS</b>	non-structural
<b>MCHR</b>	melanin-concentrating hormone receptor	<b>NSAID</b>	non-steroidal anti-inflammatory drug
<b>MDR</b>	multidrug resistance	<b>NSCLC</b>	non-small-cell lung carcinoma
<b>MDRTB</b>	multidrug-resistant tuberculosis	<b>NVOC</b>	nitroveratryloxycarbonyl
<b>MEP</b>	molecular electrostatic potential	<b>ORL1</b>	opioid receptor-like receptor
<b>miRNA</b>	micro RNA	<b>P</b>	partition coefficient
<b>miRNP</b>	micro RNA protein	<b>P<sub>2</sub>Y</b>	
<b>MMAE</b>	monomethyl auristatin E (vedotin)	<b>receptor</b>	purinergic G-protein-coupled receptor
<b>MMP</b>	matrix metalloproteinase	<b>PABA</b>	<i>p</i> -aminobenzoic acid
<b>MMPI</b>	matrix metalloproteinase inhibitor	<b>PAR</b>	protease activated receptor
<b>MOR</b>	mu opioid receptor	<b>PARP</b>	poly ADP ribose polymerase
<b>MR</b>	molar refractivity	<b>PBP</b>	penicillin binding protein
<b>mRNA</b>	messenger RNA	<b>PCP</b>	phencyclidine, otherwise known as ‘angel dust’
<b>MRSA</b>	methicillin-resistant <i>Staphylococcus aureus</i>	<b>PCT</b>	patent cooperation treaty
<b>mRTKI</b>	multi-receptor tyrosine kinase inhibitors	<b>PD-1</b>	
<b>MTP</b>	microsomal triglyceride transfer protein	<b>receptor</b>	programmed cell death 1 receptor
<b>MTDD</b>	multi-target drug discovery	<b>PDB</b>	protein data bank
<b>mTOR</b>	mechanistic or mammalian target of rapamycin	<b>PDE</b>	phosphodiesterase
<b>mTORC</b>	mechanistic or mammalian target of rapamycin complex	<b>PDGF</b>	platelet-derived growth factor
<b>mTRKI</b>	multi-tyrosine receptor kinase inhibitor	<b>PDGFR</b>	platelet-derived growth factor receptor
<b>MWt</b>	molecular weight	<b>PDK1</b>	phosphoinositide dependent kinase 1
<b>N-</b>		<b>PDT</b>	photodynamic therapy
<b>receptor</b>	nicotinic receptor	<b>PEG</b>	polyethylene glycol
<b>NA</b>	neuraminidase or noradrenaline	<b>PGE</b>	prostaglandin E
<b>NAD<sup>+</sup> /</b>		<b>PGF</b>	prostaglandin F
<b>NADH</b>	nicotinamide adenine dinucleotide	<b>PGI<sub>2</sub></b>	prostacyclin
<b>NADP<sup>+</sup> /</b>		<b>PH</b>	Pleckstrin homology
<b>NADPH</b>	nicotinamide adenine dinucleotide phosphate	<b>PI3K</b>	phosphoinositide 3-kinases
<b>NAG</b>	<i>N</i> -acetylglucosamine	<b>PIP<sub>2</sub></b>	phosphatidylinositol diphosphate
<b>NAM</b>	<i>N</i> -acetylmuramic acid	<b>PIP<sub>3</sub></b>	phosphatidylinositol (3,4,5)-triphosphate
<b>NCE</b>	new chemical entity	<b>PI</b>	protease inhibitor
<b>NDA</b>	new drug application	<b>piRNA</b>	piwi-interacting RNA
<b>NEP</b>	neutral endopeptidase	<b>PKA</b>	protein kinase A
<b>NHS</b>	National Health Service	<b>PKB</b>	protein kinase B
<b>NICE</b>	National Institute for Health and Clinical Excellence	<b>PKC</b>	protein kinase C
<b>NMDA</b>	<i>N</i> -methyl-D-aspartate	<b>PLC</b>	phospholipase C
<b>NME</b>	new molecular entity	<b>PLS</b>	partial least squares
<b>NMR</b>	nuclear magnetic resonance	<b>PPAR</b>	peroxisome proliferator-activated receptor
		<b>PPBI</b>	protein–protein binding inhibitor
		<b>PPI</b>	proton pump inhibitor



<b>PPts</b>	pyridinium 4-toluenesulphonate	<b>SPA</b>	scintillation proximity assay
<b>PTase</b>	palmitoyl transferase	<b>SPE</b>	solid-phase extraction
<b>PTCH</b>	patched receptor	<b>SPOS</b>	solution phase organic synthesis
<b>QSAR</b>	quantitative structure–activity relationships	<b>SPR</b>	surface plasmon resonance
<b>r</b>	regression or correlation coefficient	<b>ssDNA</b>	single-stranded DNA
<b>R</b>	resonance effect of an aromatic substituent in QSAR	<b>SSRI</b>	selective serotonin reuptake inhibitor
<b>RAAS</b>	renin–angiotensin–aldosterone system	<b>ssRNA</b>	single-stranded RNA
<b>RANK</b>	receptor activator of nuclear factor-kappa B	<b>STAT</b>	signal transducer and activator of transcription
<b>RCE1</b>	ras converting enzyme 1	<b>TB</b>	tuberculosis
<b>RES</b>	reticuloendothelial system	<b>TCA</b>	tricyclic antidepressants
<b>RET</b>	rearranged during transcription	<b>TFA</b>	trifluoroacetic acid
<b>RFC</b>	reduced folate carrier	<b>TGF-<math>\alpha</math></b>	transforming growth factor $\alpha$
<b>RISC</b>	RNA induced silencing complex	<b>TGF-<math>\beta</math></b>	transforming growth factor $\beta$
<b>RMSD</b>	root mean square distance	<b>THF</b>	tetrahydrofuran
<b>rRNA</b>	ribosomal RNA	<b>TM</b>	transmembrane
<b>RNA</b>	ribonucleic acid	<b>TNF</b>	tumour necrosis factor
<b>RNAi</b>	RNA interference	<b>TNFR</b>	tumour necrosis factor receptor
<b>s</b>	standard error of estimate or standard deviation	<b>TNT</b>	trinitrotoluene
<b>SAR</b>	structure–activity relationships	<b>TRAIL</b>	TNF-related apoptosis-inducing ligand
<b>SCAL</b>	safety-catch acid-labile linker	<b>TRIPS</b>	trade related aspects of intellectual property rights
<b>SCF</b>	stem cell factor	<b>tRNA</b>	transfer RNA
<b>SCFR</b>	mast/stem cell growth factor receptor	<b>T-VEC</b>	talimogene laherparepvec
<b>SCID</b>	severe combined immunodeficiency disease	<b>UTI</b>	urinary tract infection
<b>sGC</b>	soluble guanylate cyclase	<b>vdW</b>	van der Waals
<b>SH</b>	src homology	<b>VEGF</b>	vascular endothelial growth factor
<b>Shh</b>	sonic hedgehog	<b>VEGFR</b>	vascular endothelial growth factor receptor
<b>siRNA</b>	small interfering RNA	<b>VIP</b>	vasoactive intestinal peptide
<b>SKF</b>	Smith-Kline and French	<b>VOC-Cl</b>	vinylloxycarbonyl chloride
<b>Smo</b>	Smoothed receptor	<b>VRE</b>	vancomycin-resistant enterococci
<b>SNRI</b>	selective noradrenaline reuptake inhibitors	<b>VRSA</b>	vancomycin-resistant <i>Staphylococci aureus</i>
<b>siRNA</b>	Small inhibitory RNA	<b>VZV</b>	varicella-zoster viruses
<b>snRNA</b>	Small nuclear RNA	<b>WHO</b>	World Health Organization
<b>SOP</b>	standard operating procedure	<b>WTO</b>	World Trade Organization
<b>SOS</b>	son of sevenless protein		





# 1

## Drugs and drug targets: an overview

### 1.1 What is a drug?

Medicinal chemistry involves the design and synthesis of a pharmaceutical agent that has a desired biological effect on the human body or some other living system. Such a compound could also be called a 'drug', but this is a word that many scientists dislike because of the way it is viewed by society. With media headlines such as 'Drugs Menace' or 'Drug Addiction Sweeps City Streets', this is hardly surprising. However, it suggests that a distinction can be drawn between drugs that are used in medicine and drugs that are abused. But is this really true? Can we draw a neat line between 'good drugs' like penicillin and 'bad drugs' like heroin? If so, how do we define what is meant by a good or a bad drug in the first place? Where would we place a so-called social drug like cannabis in this divide? What about nicotine, or alcohol?

The answers we get depend on who we ask. As far as the law is concerned, the dividing line is defined in black and white. As far as the party-going teenager is concerned, the law is an ass. As far as we are concerned, the questions are irrelevant. Trying to divide drugs into two categories—safe or unsafe, good or bad—is futile and could even be dangerous.

First, let us consider the so-called 'good' drugs used in medicines. How 'good' are they? If a drug is to be truly 'good' it would have to do what it is meant to do, have no toxic or unwanted side effects, and be easy to take.

How many drugs fit these criteria?

The short answer is 'none'. There is no pharmaceutical compound on the market today that can completely satisfy all these conditions. Admittedly, some come quite close to the ideal. **Penicillin**, for example, has been one of the safest and most effective antibacterial agents ever discovered. Yet it too has drawbacks. It cannot treat all known bacterial infections, and, as the years have gone by, more and more bacterial strains have become resistant. Moreover, some individuals can experience severe allergic reactions to the compound.

Penicillin is a relatively safe drug, but there are some drugs that are distinctly dangerous. **Morphine** is one such example. It is an excellent analgesic, yet it suffers from serious side effects such as tolerance, respiratory depression, and addiction. It can even kill if taken in excess. **Barbiturates** are also known to be dangerous. At Pearl Harbor, American casualties were given barbiturates as general anaesthetics before surgery. However, a poor understanding of how barbiturates are stored in the body led to many patients receiving a fatal overdose. In fact, it is thought that more casualties died at the hands of the anaesthetists at Pearl Harbor than died of their wounds.

To conclude, the 'good' drugs are not as perfect as one might think.

What about the 'bad' drugs then? Is there anything good that can be said about them? Surely there is nothing we can say in defence of the highly addictive drug **heroin**?

Well, let us look at the facts about heroin. It is one of the best painkillers known to medicine. In fact, it was named heroin at the end of the nineteenth century because it was thought to be the 'heroic' drug that would banish pain for good. Heroin went on the market in 1898, but had to be withdrawn from general distribution 5 years later when its addictive properties became evident. However, heroin is still used in medicine today—under strict control, of course. The drug is called **diamorphine** and it is the drug of choice for treating patients dying of cancer. Not only does diamorphine reduce pain to acceptable levels, it also produces a euphoric effect that helps to counter the depression faced by patients close to death. Can we really condemn such a drug as being all 'bad'?

By now, it should be evident that the division between 'good' and 'bad' drugs is a woolly one and is not really relevant to our discussion of medicinal chemistry. All drugs have their good and bad points. Some have more good points than bad and vice versa, but, like people, they all have their own individual characteristics. So how are we to define a drug in general?

## 2 Chapter 1 Drugs and drug targets: an overview

One definition could be to classify drugs as ‘compounds which interact with a biological system to produce a biological response’. This definition covers all the drugs we have discussed so far, but it goes further. There are chemicals which we take every day and which have a biological effect on us. What are these everyday drugs?

One is contained in the cups of tea, coffee, and cocoa that we consume. All of these beverages contain the stimulant **caffeine**. Whenever you take a cup of coffee, you are a drug user. We could go further. Whenever you crave a cup of coffee, you are a drug addict. Even children are not immune. They get their caffeine ‘shot’ from Coke or Pepsi. Whether you like it or not, caffeine is a drug. When you take it, you experience a change of mood or feeling.

So too, if you are a worshipper of the ‘nicotine stick’. The biological effect is different. In this case you crave sedation or a calming influence, and it is the **nicotine** in the cigarette smoke which induces that effect. **Alcohol** is another example of a ‘social’ drug and, as such, causes society more problems than all other drugs put together. One only has to study road accident statistics to appreciate that fact. If alcohol was discovered today, it would probably be restricted in exactly the same way as **cocaine**. Considered in a purely scientific way, alcohol is a most unsatisfactory drug. As many will testify, it is notoriously difficult to judge the correct dose required to gain the beneficial effect of ‘happiness’ without drifting into the higher dose levels that produce unwanted side effects such as staggering down the street. Alcohol is also unpredictable in its biological effects. Either happiness or depression may result, depending on the user’s state of mind. On a more serious note, **addiction** and **tolerance** in certain individuals have ruined the lives of addicts and relatives alike.

Our definition of a drug can also be used to include less obvious compounds; for example poisons and toxins. They too interact with a biological system and produce a biological response—a bit extreme perhaps, but a response all the same. The idea of poisons acting as drugs may not appear so strange if we consider penicillin. We have no problem in thinking of penicillin as a drug, but if we were to look closely at how penicillin works, then it acts as a poison. It interacts with bacteria (the biological system) and kills them (the biological response). Fortunately for us, penicillin has no such effect on human cells.

Even those drugs which do not act as poisons have the potential to become poisons—usually if they are taken in excess. We have already seen this with morphine. At low doses it is a painkiller. At high doses, it is a poison which kills by suppressing breathing. Therefore, it is important that we treat all medicines as potential poisons and treat them with respect.

There is a term used in medicinal chemistry known as the **therapeutic index**, which indicates how safe a

particular drug is. The therapeutic index is a measure of the drug’s beneficial effects at a low dose, versus its harmful effects at a high dose. To be more precise, the therapeutic index compares the dose level required to produce toxic effects in 50% of patients to the dose level required to produce the maximum therapeutic effects in 50% of patients. A high therapeutic index means that there is a large safety margin between beneficial and toxic doses. The values for cannabis and alcohol are 1000 and 10 respectively, which might imply that cannabis is safer and more predictable than alcohol. Indeed, a cannabis preparation (**nabiximols**) has now been approved to relieve the symptoms of multiple sclerosis. However, this does not suddenly make cannabis safe. For example, the favourable therapeutic index of cannabis does not indicate its potential toxicity if it is taken over a long period of time (chronic use). For example, the various side effects of cannabis include panic attacks, paranoid delusions, and hallucinations. Clearly, the safety of drugs is a complex matter and it is not helped by media sensationalism.

If useful drugs can be poisons at high doses or over long periods of use, does the opposite hold true? Can a poison be a medicine at low doses? In certain cases, this is found to be so.

**Arsenic** is well known as a poison, but arsenic-derived compounds are used as antiprotozoal and anticancer agents. **Curare** is a deadly poison which was used by the native people of South America to tip their arrows such that a minor arrow wound would be fatal, yet compounds based on the **tubocurarine** structure (the active principle of curare) are used in surgical operations to relax muscles. Under proper control and in the correct dosage, a lethal poison may well have an important medical role. Alternatively, lethal poisons can be the starting point for the development of useful drugs. For example, ACE inhibitors are important cardiovascular drugs that were developed, in part, from the structure of a snake venom.

Since our definition covers any chemical that interacts with any biological system, we can include all the pesticides used in agriculture as drugs. They interact with the biological systems of harmful bacteria, fungi, and insects to produce a toxic effect that protects plants.

Even food can act like a drug. Junk foods and fizzy drinks have been blamed for causing hyperactivity in children. It is believed that junk foods have high concentrations of certain amino acids which can be converted in the body to neurotransmitters—chemicals that pass messages between nerves. In excess, these chemical messengers overstimulate the nervous system, leading to the disruptive behaviour observed in susceptible individuals. Allergies due to food additives and preservatives are also well recorded.

Some foods even contain toxic chemicals. Broccoli, cabbage, and cauliflower all contain high levels of a

chemical that can cause reproductive abnormalities in rats. Peanuts and maize sometimes contain fungal toxins, and it is thought that fungal toxins in food were responsible for one of the biblical plagues. Basil contains over 50 compounds that are potentially carcinogenic, and other herbs contain some of the most potent carcinogens known. Carcinogenic compounds have also been identified in radishes, brown mustard, apricots, cherries, and plums. Such unpalatable facts might put you off your dinner, but take comfort—these chemicals are present in such small quantities that the risk is insignificant. Therein lies a great truth, which was recognized as long ago as the fifteenth century when it was stated that ‘Everything is a poison, nothing is a poison. It is the dose that makes the poison.’

Almost anything taken in excess will be toxic. You can make yourself seriously ill by taking 100 aspirin tablets or a bottle of whisky or 9 kg of spinach. The choice is yours!

To conclude, drugs can be viewed as actual or potential poisons. An important principle is that of **selective toxicity**. Many drugs are effective because they are toxic to ‘problem cells’, but not normal cells. For example, antibacterial, antifungal, and antiprotozoal drugs are useful in medicine when they show a selective toxicity to microbial cells, rather than mammalian cells. Clinically effective anticancer agents show a selective toxicity for cancer cells over normal cells. Similarly, effective antiviral agents are toxic to viruses rather than normal cells.

Having discussed what drugs are, we shall now consider why, where, and how they act.

#### KEY POINTS

- Drugs are compounds that interact with a biological system to produce a biological response.
- No drug is totally safe. Drugs vary in the side effects they might have.
- The dose level of a compound determines whether it will act as a medicine or as a poison.
- The therapeutic index is a measure of a drug’s beneficial effect at a low dose versus its harmful effects at a higher dose. A high therapeutic index indicates a large safety margin between beneficial and toxic doses.
- The principle of selective toxicity means that useful drugs show toxicity against foreign or abnormal cells, but not against normal host cells.

## 1.2 Drug targets

Why should chemicals, some of which have remarkably simple structures, have such an important effect on such

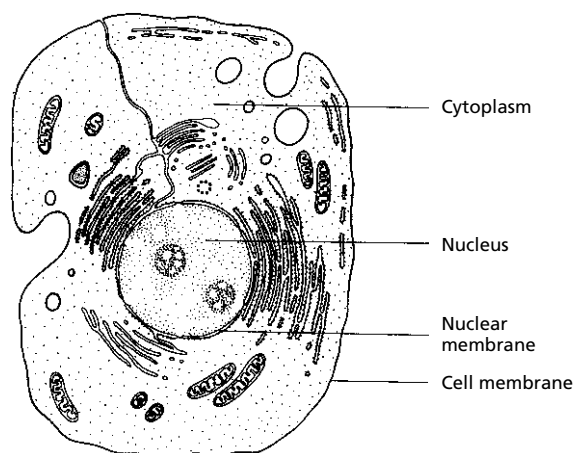
a complicated and large structure as a human being? The answer lies in the way that the human body operates. If we could see inside our bodies to the molecular level, we would see a magnificent array of chemical reactions taking place, keeping the body healthy and functioning.

Drugs may be mere chemicals, but they are entering a world of chemical reactions with which they interact. Therefore, there should be nothing odd in the fact that they can have an effect. The surprising thing might be that they can have such *specific* effects. This is more a result of *where* they act in the body—the drug targets.

### 1.2.1 Cell structure

Since life is made up of cells, then quite clearly drugs must act on cells. The structure of a typical mammalian cell is shown in Fig. 1.1. All cells in the human body contain a boundary wall called the **cell membrane** which encloses the contents of the cell—the **cytoplasm**. The cell membrane seen under the electron microscope consists of two identifiable layers, each of which is made up of an ordered row of phosphoglyceride molecules such as **phosphatidylcholine (lecithin)** (Fig. 1.2). The outer layer of the membrane is made up of phosphatidylcholine whereas the inner layer is made up of phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Each phosphoglyceride molecule consists of a small polar head-group, and two long hydrophobic (water-hating) chains.

In the cell membrane, the two layers of phospholipids are arranged such that the hydrophobic tails point towards each other and form a fatty, hydrophobic centre, while the ionic head-groups are placed at the inner and outer surfaces of the cell membrane (Fig. 1.3). This is a stable structure because the ionic, hydrophilic head-groups



**FIGURE 1.1** A typical mammalian cell. Taken from J. Mann, *Murder, magic, and medicine*, Oxford University Press (1992), with permission.

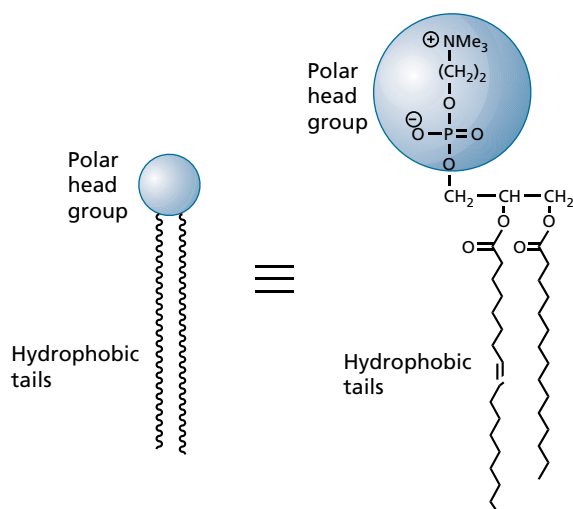


FIGURE 1.2 Phosphoglyceride structure.

interact with the aqueous media inside and outside the cell, whereas the hydrophobic tails maximize hydrophobic interactions with each other and are kept away from the aqueous environments. The overall result of this structure is to construct a fatty barrier between the cell's interior and its surroundings.

The membrane is not just made up of phospholipids, however. There are a large variety of proteins situated in the cell membrane (Fig. 1.3). Some proteins lie attached to the inner or the outer surface of the membrane. Others are embedded in the membrane with part of their structure exposed to one surface or both. The extent to which these proteins are embedded within the cell membrane structure depends on the types of amino acid present. Portions of protein that are embedded in the cell membrane have a large number of hydrophobic amino acids, whereas those portions that stick out from the surface have a large number of hydrophilic amino acids. Many surface proteins also have short chains of carbohydrates attached to them and are thus classed as **glycoproteins**.

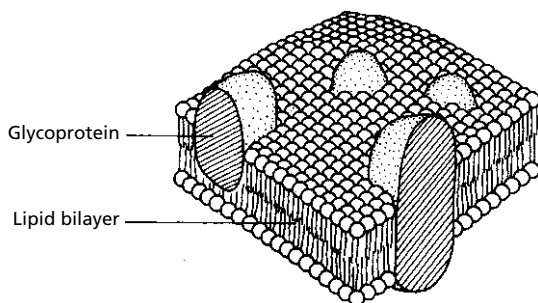


FIGURE 1.3 Cell membrane. Taken from J. Mann, *Murder, magic, and medicine*, Oxford University Press (1992), with permission.

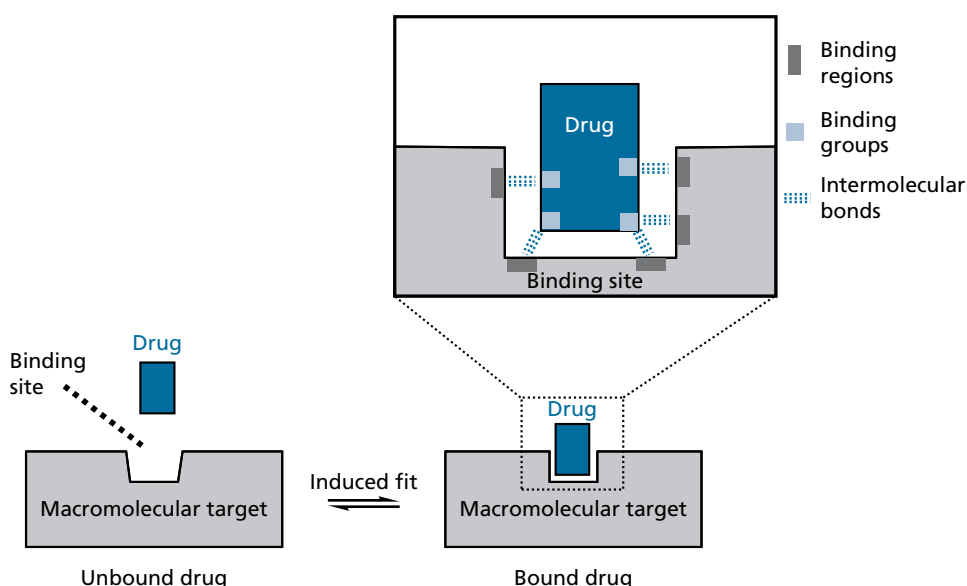
These carbohydrate segments are important to cell–cell recognition (section 10.7).

Within the cytoplasm there are several structures, one of which is the **nucleus**. This acts as the ‘control centre’ for the cell. The nucleus contains the genetic code—the DNA—which acts as the blueprint for the construction of all the cell's proteins. There are many other structures within a cell, such as the mitochondria, the Golgi apparatus, and the endoplasmic reticulum, but it is not the purpose of this book to look at the structure and function of these organelles. Suffice it to say that different drugs act on molecular targets at different locations in the cell.

## 1.2.2 Drug targets at the molecular level

We shall now move to the molecular level, because it is here that we can truly appreciate how drugs work. The main molecular targets for drugs are proteins (enzymes, receptors, and transport proteins), and nucleic acids (DNA and RNA). These are large molecules (**macromolecules**) having molecular weights measured in the order of several thousand atomic mass units. They are much bigger than a typical drug, which has a molecular weight in the order of a few hundred atomic mass units.

The interaction of a drug with a macromolecular target involves a process known as **binding**. There is usually a specific area of the macromolecule where this takes place, and this is known as the **binding site** (Fig. 1.4). Typically, this takes the form of a hollow or canyon on 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 bonds**; see for example protein structure, sections 2.2 and 2.3). None of these bonds is as strong as the covalent bonds that make up the skeleton of a molecule, and so they can be formed, then broken again. This means that an equilibrium takes place between the drug being bound and unbound to its target. The binding forces are strong enough to hold the drug for a certain period of time to let it have an effect on the target, but weak enough to allow it to depart once it has done its job. The length of time the drug remains at its target will depend on the number of intermolecular bonds involved in holding it there. Drugs having a large number of interactions are likely to remain bound longer than those that have only a few. The relative strength of the different intermolecular binding forces



**FIGURE 1.4** The equilibrium of a drug being bound and unbound to its target.

is also an important factor. Functional groups present in the drug can be important in forming intermolecular bonds with the target binding site. If they do so, they are called **binding groups**. However, the carbon skeleton of the drug also plays an important role in binding the drug to its target through van der Waals interactions. As far as the target binding site is concerned, it too contains functional groups and carbon skeletons which can form intermolecular bonds 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 and produce a pharmacological effect is known as **pharmacodynamics**. Let us now consider the types of intermolecular bond that are possible.

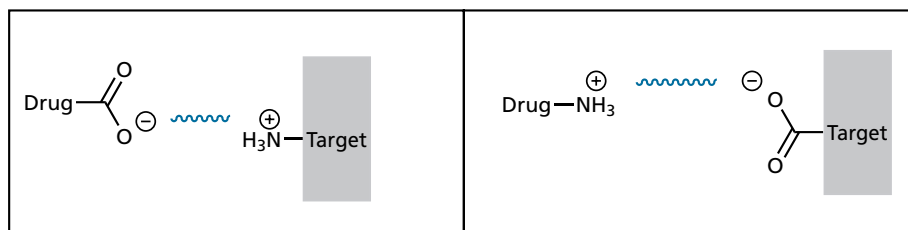
### 1.3 Intermolecular bonding forces

There are several types of intermolecular bonding interactions, which differ in their bond strengths. The number and types of these interactions depend on the structure

of the drug and the functional groups that are present (section 13.1 and Appendix 7). Thus, each drug may use one or more of the following interactions, but not necessarily all of them.

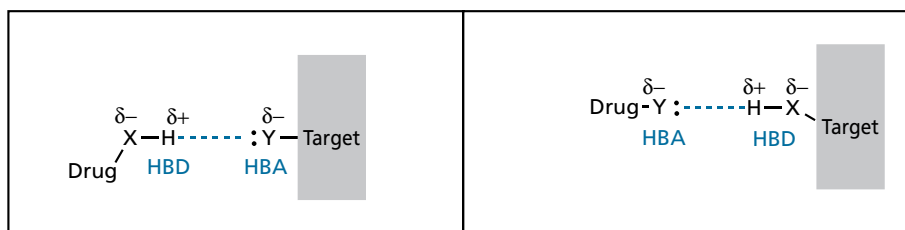
#### 1.3.1 Electrostatic or ionic bonds

An ionic or electrostatic bond is the strongest of the intermolecular bonds ( $20\text{--}40\text{ kJ mol}^{-1}$ ) and takes place between groups having opposite charges such as a carboxylate ion and an aminium ion (Fig. 1.5). The strength of the interaction is inversely proportional to the distance between the two charged atoms, and it is also dependent on the nature of the environment, being stronger in hydrophobic environments than in polar environments. Usually, the binding sites of macromolecules are more hydrophobic in nature than the surface, and so this enhances the effect of an ionic interaction. The drop-off in ionic bonding strength with separation is less than in other intermolecular interactions, so if an ionic interaction is possible, it is likely to be the most important initial interaction as the drug enters the binding site.



**FIGURE 1.5** Electrostatic (ionic) interactions between a drug and the binding site.





**FIGURE 1.6** Hydrogen bonding shown by a dashed line between a drug and a binding site (X, Y = oxygen or nitrogen; HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

### 1.3.2 Hydrogen bonds

A hydrogen bond can vary substantially in strength, and normally takes place between an electron-rich heteroatom and an electron-deficient hydrogen (Fig. 1.6). The electron-rich heteroatom has to have a lone pair of electrons and is usually oxygen or nitrogen.

The electron-deficient hydrogen is usually linked by a covalent bond to an electronegative atom, such as oxygen or nitrogen. As the electronegative atom (X) has a greater attraction for electrons, the electron distribution in the covalent bond (X–H) is weighted towards the more electronegative atom, and so the hydrogen gains a slight positive charge. Such a hydrogen atom can act as a **hydrogen bond donor (HBD)**. The electron-rich heteroatom that receives the hydrogen bond is known as the **hydrogen bond acceptor (HBA)**. Some functional groups can provide both hydrogen bond donors and hydrogen bond acceptors (e.g. OH, NH<sub>2</sub>). When such a group is present in a binding site, it is possible that it might bind to one ligand as a hydrogen bond donor and to another as a hydrogen bond acceptor. This characteristic is given the term **hydrogen bond flip-flop**.

Hydrogen bonds have been viewed as a weak form of electrostatic interaction, because the heteroatom is slightly negative and the hydrogen is slightly positive. However, there is more to hydrogen bonding than an attraction between partial charges. Unlike other intermolecular interactions, an interaction of orbitals takes place between the two molecules (Fig. 1.7). The orbital containing the lone pair of electrons on heteroatom Y interacts with the atomic orbitals normally involved in the covalent bond between X and H. This results in a weak form of sigma ( $\sigma$ ) bonding and has an important directional consequence

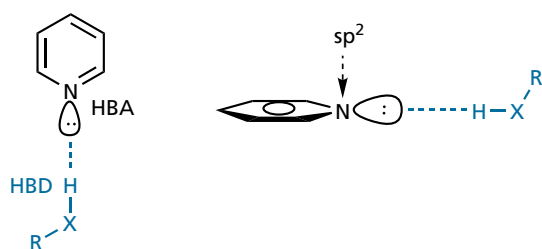
that is not evident in electrostatic bonds. The optimum orientation is where the X–H bond points directly to the lone pair on Y, such that the angle formed between X, H, and Y is 180°. This is observed in very strong hydrogen bonds. However, the angle can vary between 130° and 180° for moderately strong hydrogen bonds, and can be as low as 90° for weak hydrogen bonds. The lone pair orbital of Y also has a directional property, depending on its hybridization. For example, the nitrogen of a pyridine ring is sp<sup>2</sup> hybridized and so the lone pair points directly away from the ring, and in the same plane (Fig. 1.8). The best location for a hydrogen bond donor would be the region of space indicated in the figure.

The strength of a hydrogen bond can vary widely, but most hydrogen bonds in drug–target interactions are moderate in strength, varying from 16 to 60 kJ mol<sup>−1</sup>—approximately 10 times less than a covalent bond. The bond distance reflects this, and hydrogen bonds are typically 1.5–2.2 Å compared with 1.0–1.5 Å for a covalent bond. The strength of a hydrogen bond depends on the strengths of the hydrogen bond acceptor and the hydrogen bond donor. A good hydrogen bond acceptor has to be electronegative and have a lone pair of electrons. Nitrogen and oxygen are the most common atoms involved as hydrogen bond acceptors in biological systems. Nitrogen has one lone pair of electrons and can act as an acceptor for one hydrogen bond; oxygen has two lone pairs of electrons and can act as an acceptor for two hydrogen bonds (Fig. 1.9).

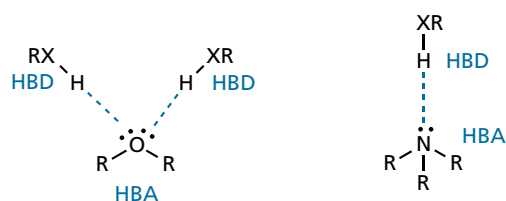
Several drugs and macromolecular targets contain a sulphur atom, which is also electronegative. However, sulphur is a weak hydrogen bond acceptor because its lone pairs are in third-shell orbitals, which are larger and more diffuse than second-shell orbitals. This means that



**FIGURE 1.7** Orbital overlap in a hydrogen bond.



**FIGURE 1.8** Directional influence of hybridization on hydrogen bonding.



**FIGURE 1.9** Oxygen and nitrogen acting as hydrogen bond acceptors (HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

the orbitals concerned interact less efficiently with the small 1s orbital of a hydrogen atom.

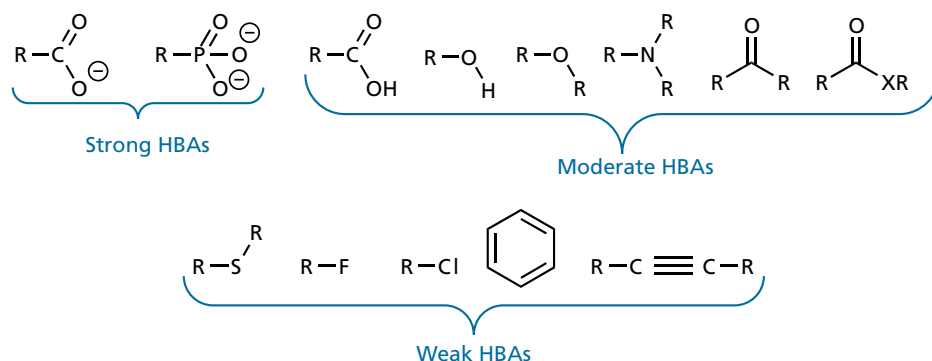
Fluorine, which is present in several drugs, is more electronegative than either oxygen or nitrogen. It also has three lone pairs of electrons, and this might suggest that it would make a good hydrogen bond acceptor. In fact, it is rather a weak hydrogen bond acceptor. It has been suggested that fluorine is so electronegative that it clings on tightly to its

lone pairs of electrons, making them incapable of hydrogen bond interactions. This is in contrast to a fluoride ion which is a very strong hydrogen bond acceptor.

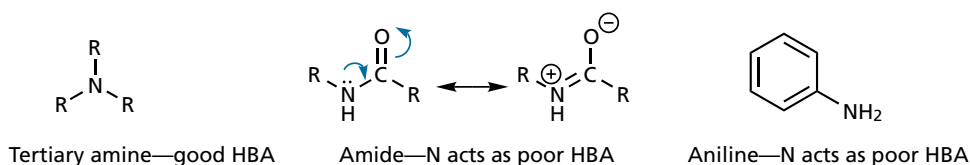
Any feature that affects the electron density of the hydrogen bond acceptor is likely to affect its ability to act as a hydrogen bond acceptor; the greater the electron density of the heteroatom the greater its strength as a hydrogen bond acceptor. For example, the oxygen of a negatively charged carboxylate ion is a stronger hydrogen bond acceptor than the oxygen of the uncharged carboxylic acid (Fig. 1.10). Phosphate ions can also act as good hydrogen bond acceptors. Most hydrogen bond acceptors present in drugs and binding sites are neutral functional groups such as ethers, alcohols, phenols, amides, amines, and ketones. These groups will form moderately strong hydrogen bonds.

It has been proposed that the pi ( $\pi$ ) systems present in alkynes and aromatic rings are regions of high electron density and can act as hydrogen bond acceptors. However, the electron density in these systems is diffuse, and so the hydrogen bonding interaction is much weaker than those involving oxygen or nitrogen. As a result, aromatic rings and alkynes are only likely to be significant hydrogen bond acceptors if they interact with a strong hydrogen bond donor such as an alkylammonium ion ( $\text{NHR}_3^+$ ).

More subtle effects can influence whether an atom is a good hydrogen bond acceptor or not. For example, the nitrogen atom of an aliphatic tertiary amine is a better hydrogen bond acceptor than the nitrogen of an amide or an aniline (Fig. 1.11). In the latter functional groups,

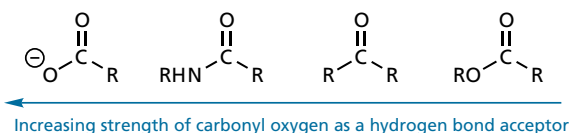


**FIGURE 1.10** Relative strengths of hydrogen bond acceptors (HBAs).

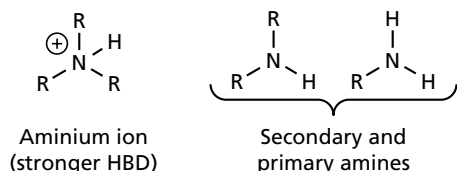


**FIGURE 1.11** Comparison of different nitrogen-containing functional groups as hydrogen bond acceptors (HBAs).





**FIGURE 1.12** Comparison of carbonyl oxygens as hydrogen bond acceptors.



**FIGURE 1.13** Comparison of hydrogen bond donors (HBDs).

the lone pair of the nitrogen can interact with neighbouring pi systems to form various resonance structures. As a result, it is less likely to take part in a hydrogen bond.

Similarly, the ability of a carbonyl group to act as a hydrogen bond acceptor varies depending on the functional group involved (Fig. 1.12).

It has also been observed that an  $sp^3$  hybridized oxygen atom linked to an  $sp^2$  carbon atom rarely acts as an HBA. This includes the alkoxy oxygen of esters, and the oxygen atom present in aromatic ethers or furans.

Good hydrogen bond donors contain an electron-deficient proton linked to oxygen or nitrogen. The more electron-deficient the proton, the better it will act as a hydrogen bond donor. For example, a proton attached to a positively charged nitrogen atom acts as a stronger hydrogen bond donor than the proton of a primary or secondary amine (Fig. 1.13). Because the nitrogen is positively charged, it has a greater pull on the electrons surrounding it, making attached protons even more electron-deficient.

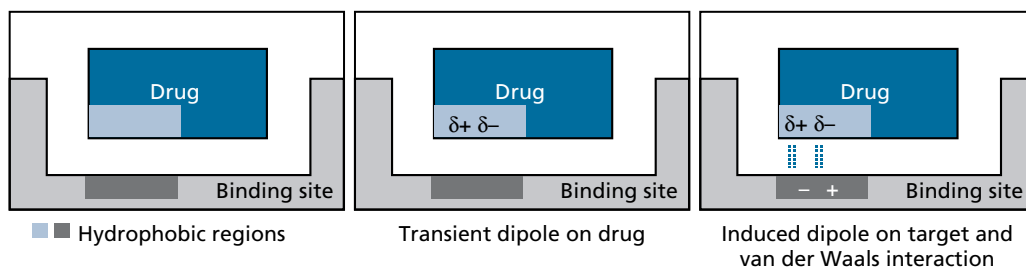
### 1.3.3 Van der Waals interactions

Van der Waals interactions are very weak interactions that are typically  $2\text{--}4\text{ kJ mol}^{-1}$  in strength. They involve

interactions between hydrophobic regions of different molecules, such as aliphatic substituents or the overall carbon skeleton. The electronic distribution in neutral, non-polar regions is never totally even or symmetrical, and there are always transient areas of high and low electron densities leading to temporary dipoles. The dipoles in one molecule can induce dipoles in a neighbouring molecule, leading to weak interactions between the two molecules (Fig. 1.14). Thus, an area of high electron density on one molecule can have an attraction for an area of low electron density on another molecule. The strength of these interactions falls off rapidly the further the two molecules are apart, decreasing to the seventh power of the separation. Therefore, the drug has to be close to the target binding site before the interactions become important. Van der Waals interactions are also referred to as **London forces**. Although the interactions are individually weak, there may be many such interactions between a drug and its target, and so the overall contribution of van der Waals interactions is often crucial to binding. Hydrophobic forces are also important when the non-polar regions of molecules interact (section 1.3.6).

### 1.3.4 Dipole–dipole and ion–dipole interactions

Many molecules have a permanent dipole moment resulting from the different electronegativities of the atoms and functional groups present. For example, a ketone has a dipole moment due to the different electronegativities of the carbon and oxygen making up the carbonyl bond. The binding site also contains functional groups, so it is inevitable that it too will have various local dipole moments. It is possible for the dipole moments of the drug and the binding site to interact as a drug approaches, aligning the drug such that the dipole moments are parallel and in opposite directions (Fig. 1.15). If this positions the drug such that other intermolecular interactions can take place between the drug and the binding site, then the alignment is beneficial to both binding and activity. If not, then binding and activity may be weakened. An example of such an effect can be found in anti-ulcer drugs (section 25.2.8.3).



**FIGURE 1.14** Van der Waals interactions between hydrophobic regions of a drug and a binding site.

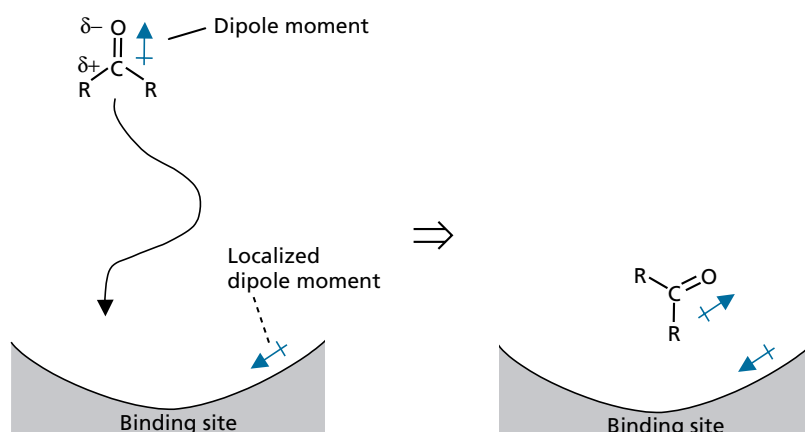


FIGURE 1.15 Dipole–dipole interactions between a drug and a binding site.

The strength of dipole–dipole interactions reduces with the cube of the distance between the two dipoles. This means that dipole–dipole interactions fall away more quickly with distance than electrostatic interactions, but less quickly than van der Waals interactions.

An ion–dipole interaction is where a charged or ionic group in one molecule interacts with a dipole in a second molecule (Fig. 1.16). This is stronger than a dipole–dipole interaction, and falls off less rapidly with separation (decreasing relative to the square of the separation).

Interactions involving an induced dipole moment have been proposed. There is evidence that an aromatic ring can interact with an ionic group such as a quaternary ammonium ion. Such an interaction is feasible if the positive

charge of the quaternary ammonium group distorts the  $\pi$  electron cloud of the aromatic ring to produce a dipole moment, where the face of the aromatic ring is electron-rich and the edges are electron-deficient (Fig. 1.17). This is also called a **cation– $\pi$  interaction**. An important neurotransmitter called **acetylcholine** forms this type of interaction with its binding site (section 22.5).

### 1.3.5 Repulsive interactions

So far we have concentrated on attractive forces, which increase in strength the closer the molecules approach each other. Repulsive interactions are also important. Otherwise, there would be nothing to stop molecules

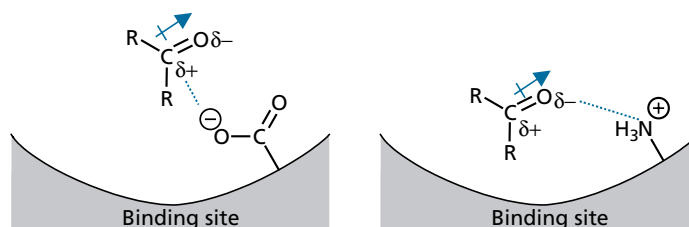


FIGURE 1.16 Ion–dipole interactions between a drug and a binding site.

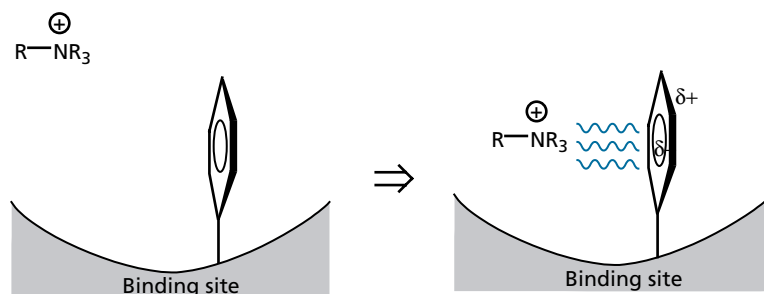


FIGURE 1.17 Induced dipole interaction between an alkylammonium ion and an aromatic ring.

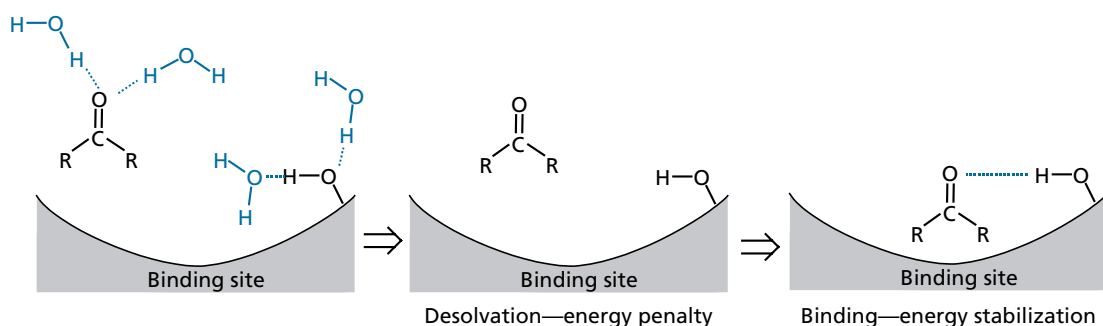


FIGURE 1.18 Desolvation of a drug and its target binding site prior to binding.

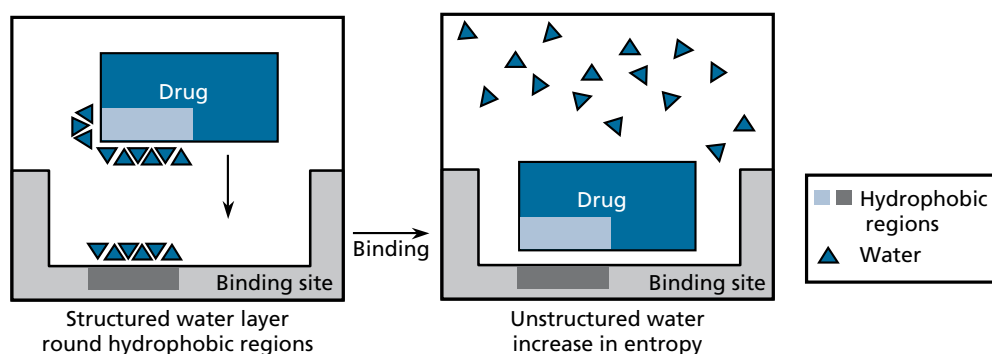


FIGURE 1.19 Hydrophobic interactions.

trying to merge with each other! If molecules come too close, their molecular orbitals start to overlap and this results in repulsion. Other forms of repulsion are related to the types of groups present in both molecules. For example, two charged groups of identical charge are repelled.

### 1.3.6 The role of water and hydrophobic interactions

A crucial feature that is often overlooked when considering the interaction of a drug with its target is the role of water. The macromolecular targets in the body exist in an aqueous environment, and the drug has to travel through that environment in order to reach its target. Therefore, both the drug and the macromolecule are solvated with water molecules before they meet each other. The water molecules surrounding the drug and the target binding site have to be stripped away before the interactions described above can take place (Fig. 1.18). This requires energy, and if the energy required to desolvate both the drug and the binding site is greater than the stabilization energy gained by the binding interactions, then the drug may be ineffective. In certain cases, it has even proved beneficial to remove a polar binding group from a drug in order to lower its energy of desolvation. For example, a polar binding group was removed during the development of the antiviral drug **ritonavir** (section 20.7.4.4).

Sometimes polar groups are added to a drug to increase its water solubility. If this is the case, it is important that such groups are positioned in such a way that they protrude from the binding site when the drug binds; in other words they are solvent-accessible or solvent-exposed. In this way, the water that solvates this highly polar group does not have to be stripped away, and there is no energy penalty when the drug binds to its target. Examples of this can be seen in sections 21.6.2.1, 26.9.1.2, and Case study 5.

It is not possible for water to solvate the non-polar or hydrophobic regions of a drug or its target binding site. Instead, the surrounding water molecules form stronger than usual interactions with each other, resulting in an ordered layer of water next to the non-polar surface. This represents a negative entropy due to the increase in order. When the hydrophobic region of a drug interacts with a hydrophobic region of a binding site, these water molecules are freed and become less ordered (Fig. 1.19). This leads to an increase in entropy and a gain in binding energy.<sup>1</sup> The interactions involved are small, at 0.1–0.2 kJ mol<sup>-1</sup> for each square angstrom of hydrophobic surface, but overall they can be substantial. Sometimes, a hydrophobic region in the drug may not be sufficiently close to a

<sup>1</sup>The free energy gained by binding ( $\Delta G$ ) is related to the change in entropy ( $\Delta S$ ) by the equation  $\Delta G = \Delta H - T\Delta S$ . If entropy increases,  $\Delta S$  is positive which makes  $\Delta G$  more negative. The more negative the value of  $\Delta G$ , the more likely binding will take place.

hydrophobic region in the binding site, and water may be trapped between the two surfaces. The entropy increase is not so substantial in that case, and there is a benefit in designing a better drug that fits more snugly.

## 1.4 Pharmacokinetic issues and medicines

Pharmacodynamics is the study of how a drug binds to its target binding site and produces a pharmacological effect. However, a drug capable of binding to a particular target is not necessarily going to be useful as a clinical agent or medicine. For that to be the case, the drug not only has to bind to its target, it has to reach it in the first place. For an orally administered drug, that involves a long journey with many hazards to be overcome. The drug has to survive stomach acids, then digestive enzymes in the intestine. It has to be absorbed from the gut into the blood supply, then it has to survive the liver where enzymes try to destroy it (drug metabolism). It has to be distributed round the body and not get mopped up by fat tissue. It should not be excreted too rapidly or else frequent doses will be required to maintain activity. On the other hand, it should not be excreted too slowly or its effects could linger on longer than required. The study of how a drug is absorbed, distributed, metabolized, and excreted (known as ADME in the pharmaceutical industry) is called **pharmacokinetics**. Pharmacokinetics has sometimes been described as ‘what the body does to the drug’ as opposed to pharmacodynamics—‘what the drug does to the body’.

There are many ways in which medicinal chemists can design a drug to improve its pharmacokinetic properties, but the methods by which a drug is formulated and administered are just as important. Medicines are not just composed of the active pharmaceutical agent. For example, a pill contains a whole range of chemicals which are present to give structure and stability to the pill, and also to aid the delivery and breakdown of the pill at the desired part of the gastrointestinal tract.

### KEY POINTS

- Drugs act on molecular targets located in the cell membrane of cells or within the cells themselves.
- Drug targets are macromolecules that have a binding site into which the drug fits and binds.
- Most drugs bind to their targets by means of intermolecular bonds.
- Pharmacodynamics is the study of how drugs interact with their targets and produce a pharmacological effect.
- Electrostatic or ionic interactions occur between groups of opposite charge.
- Hydrogen bonds occur between an electron-rich heteroatom and an electron-deficient hydrogen.
- The hydrogen involved in a hydrogen bond is called the hydrogen bond donor. The electronegative atom that interacts with the hydrogen in a hydrogen bond is called the hydrogen bond acceptor.
- Van der Waals interactions take place between non-polar regions of molecules and are caused by transient dipole–dipole interactions.
- Ion–dipole and dipole–dipole interactions are a weak form of electrostatic interaction.
- Hydrophobic interactions involve the displacement of ordered layers of water molecules which surround hydrophobic regions of molecules. The resulting increase in entropy contributes to the overall binding energy.
- Polar groups have to be desolvated before intermolecular interactions take place. This results in an energy penalty.
- The pharmacokinetics of a drug relate to its absorption, distribution, metabolism, and excretion in the body.

## 1.5 Classification of drugs

There are four main ways in which drugs might be classified or grouped.

**By pharmacological effect.** Drugs can be classified depending on the biological or pharmacological effect that they have; for example analgesics, antipsychotics, antihypertensives, anti-asthmatics, and antibiotics. This is useful if one wishes to know the full scope of drugs available for a certain ailment, but it means that the drugs included are numerous and highly varied in structure. This is because there are a large variety of targets at which drugs could act in order to produce the desired effect. It is, therefore, not possible to compare different painkillers and expect them to look alike or to have some common mechanism of action.

The chapters on antibacterial, antiviral, anticancer, anti-ulcer, and cardiovascular drugs (Chapters 19, 20, 21, 25, and 26) illustrate the variety of drug structures and mechanisms of action that are possible when drugs are classified according to their pharmacological effect.

**By chemical structure.** Many drugs which have a common skeleton are grouped together; for example penicillins, barbiturates, opiates, steroids, and catecholamines. In some cases, this is a useful classification since the biological activity and mechanism of action is the same for the structures involved; for example, the antibiotic activity of penicillins. However, not all compounds with similar chemical structure have the same biological action. For example, steroids share a similar tetracyclic structure, but they have very different effects in the body. In this text, various groups of structurally related drugs are discussed; for example, penicillins, cephalosporins, sulphonamides,

opioids, and glucocorticoids (sections 19.4–19.5, Chapter 24, and Case study 6). These are examples of compounds with a similar structure and similar mechanism of action. However, there are exceptions. Most sulphonamides are used as antibacterial agents, but there are a few which have totally different medical applications.

**By target system.** Drugs can be classified according to whether they affect a certain target system in the body. An example of a target system is where a neurotransmitter is synthesized, released from its neuron, interacts with a protein target, and is either metabolized or reabsorbed into the neuron. This classification is a bit more specific than classifying drugs by their overall pharmacological effect. However, there are still several different targets with which drugs could interact in order to interfere with the system, and so the drugs included in this category are likely to be quite varied in structure due to the different mechanisms of action that are involved. In Chapters 22 and 23, we look at drugs that act on target systems—the cholinergic and the adrenergic system respectively.

**By target molecule.** Some drugs are classified according to the molecular target with which they interact. For example, anticholinesterases (sections 22.12–22.15) are drugs which act by inhibiting the enzyme acetylcholinesterase. This is a more specific classification since we have now identified the precise target at which the drugs act. In this situation, we might expect some structural similarity between the agents involved and a common mechanism of action, although this is not an inviolable assumption. However, it is easy to lose the wood for the trees and to lose sight of why it is useful to have drugs which switch off a particular enzyme or receptor. For example, it is not intuitively obvious why an anticholinesterase agent could be useful in treating Alzheimer's disease or glaucoma.

## 1.6 Naming of drugs and medicines

The vast majority of chemicals that are synthesized in medicinal chemistry research never make it to the market place and it would be impractical to name them all. Instead, research groups label them with a code which usually consists of letters and numbers. The letters are specific to the research group undertaking the work, and the number is specific for the compound. Thus, Ro31-8959, ABT-538, and MK-639 were compounds prepared by Roche, Abbott, and Merck pharmaceuticals respectively. If the compounds concerned show promise as therapeutic drugs, they are taken forward to pre-clinical trials then clinical studies, by which time they are often named. For example, the above compounds showed promise as anti-HIV drugs and were named **saquinavir**, **ritonavir**, and **indinavir** respectively. Finally, if the drugs prove successful and are marketed as medicines, they are given a proprietary,

brand, or trade name which only the company can use. For example, the above compounds were marketed as **Fortovase**<sup>®</sup>, **Norvir**<sup>®</sup>, and **Crixivan**<sup>®</sup> respectively (note that brand names always start with a capital letter and have the symbol R or TM to indicate that they are registered brand names). The proprietary names are also specific for the preparation or formulation of the drug. For example, Fortovase<sup>®</sup> (or Fortovase<sup>™</sup>) is a preparation containing 200 mg of saquinavir in a gel-filled, beige-coloured capsule. If the formulation is changed, then a different name is used. For example, Roche sell a different preparation of saquinavir called **Invirase**<sup>®</sup> which consists of a brown/green capsule containing 200 mg of saquinavir as the mesylate salt. When a drug's patent has expired, it is possible for any pharmaceutical company to produce and sell that drug as a generic medicine. However, they are not allowed to use the trade name used by the company that originally invented it. European law requires that generic medicines are given a **recommended International Non-proprietary Name** (rINN) which is usually identical to the name of the drug. In Britain, such drugs were given a **British Approved Name** (BAN), but these have now been modified to fall in line with rINNs. rINNs generally have a suffix which indicates the therapeutic area for the named drug. For example, saquinavir, ritonavir, and indinavir all end with the suffix -vir indicating that they are antiviral agents.

Since the naming of drugs is progressive, early research papers in the literature may only use the original letter/number code since the name of the drug had not been allocated at the time of publication.

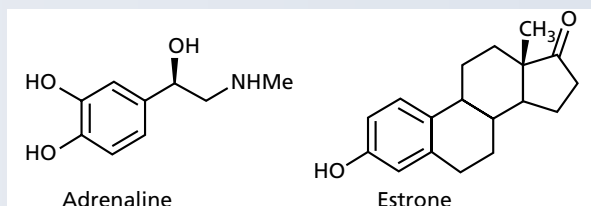
Throughout this text, the names of the active constituents are used rather than the trade names, although the trade name may be indicated if it is particularly well known. For example, it is indicated that **sildenafil** is **Viagra**<sup>®</sup> and that **paclitaxel** is **Taxol**<sup>®</sup>. If you wish to find out the trade name for a particular drug, these are listed in the index. If you wish to 'go the other way', Appendix 6 contains trade names and directs you to the relevant compound name. Only those drugs covered in the text are included and if you cannot find the drug you are looking for, you should refer to other textbooks or formularies such as the British National Formulary (see General further reading).

### KEY POINTS

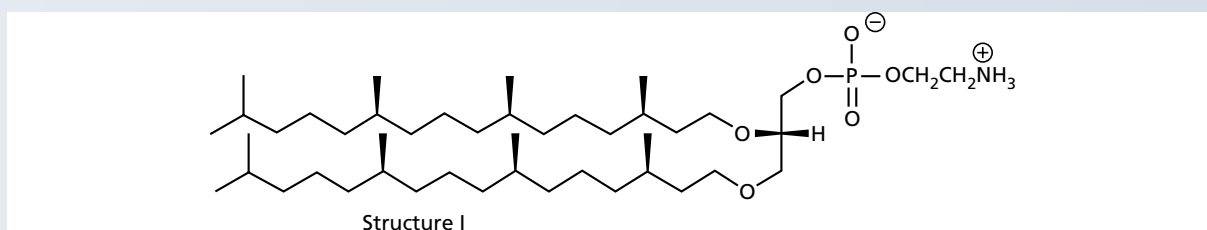
- Drugs can be classified by their pharmacological effect, their chemical structure, their effect on a target system, or their effect on a target structure.
- Clinically useful drugs have a trade (or brand) name, as well as a recommended international non-proprietary name.
- Most structures produced during the development of a new drug are not considered for the clinic. They are identified by simple codes that are specific to each research group.

## QUESTIONS

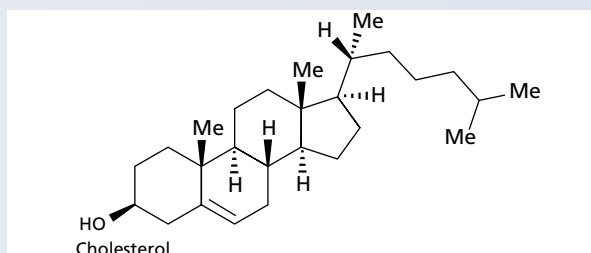
1. The hormone adrenaline interacts with proteins located on the surface of cells and does not cross the cell membrane. However, larger steroid molecules such as estrone cross cell membranes and interact with proteins located in the cell nucleus. Why is a large steroid molecule able to cross the cell membrane when a smaller molecule such as adrenaline cannot?



2. Valinomycin is an antibiotic which is able to transport ions across cell membranes and disrupt the ionic balance of the cell. Find out the structure of valinomycin and explain why it is able to carry out this task.
3. Archaea are microorganisms which can survive in extreme environments such as high temperature, low pH, or high salt concentration. It is observed that the cell membrane phospholipids in these organisms (see structure I) are markedly different from those in eukaryotic cell membranes. What differences are present and what function might they serve?



4. Teicoplanin is an antibiotic which 'caps' the building blocks used in the construction of the bacterial cell wall, such that they cannot be linked up. The cell wall is a barrier surrounding the bacterial cell membrane, and the building blocks are anchored to the outside of this cell membrane prior to their incorporation into the cell wall. Teicoplanin contains a very long alkyl substituent which plays no role in the capping mechanism. However, if this substituent is absent, activity drops. What role do you think this alkyl substituent might serve?
5. The Ras protein is an important protein in signalling processes within the cell. It exists freely in the cell cytoplasm, but must become anchored to the inner surface of the cell membrane in order to carry out its function. What kind of modification to the protein might take place to allow this to happen?
6. Cholesterol is an important constituent of eukaryotic cell membranes and affects the fluidity of the membrane. Consider the structure of cholesterol (shown below) and suggest how it might be orientated in the membrane.
7. Most unsaturated alkyl chains in phospholipids are *cis* rather than *trans*. Consider the *cis*-unsaturated alkyl chain in the phospholipid shown in Fig. 1.2. Redraw this chain to give a better representation of its shape and compare it with the shape of its *trans*-isomer. What conclusions can you make regarding the packing of such chains in the cell membrane, and the effect on membrane fluidity?
8. The relative strength of carbonyl oxygens as hydrogen bond acceptors is shown in Fig. 1.12. Suggest why the order is as shown.
9. Consider the structures of adrenaline, estrone, and cholesterol and suggest what kind of intermolecular interactions are possible for these molecules and where they occur.
10. Using the index and Appendix 8 (on the website), identify the structures and trade names for the following drugs—amoxicillin, ranitidine, gefitinib, atracurium.



Multiple-choice questions are available on the Online Resource Centre at [www.oxfordtextbooks.co.uk/orc/patrick6e/](http://www.oxfordtextbooks.co.uk/orc/patrick6e/)



## FURTHER READING

Kubinyi, H. (2001) Hydrogen bonding: The last mystery in drug design? in Testa, B., van de Waterbeemd, H., Folkers, G., and Guy, R. (eds), *Pharmacokinetic optimization in drug research*. Wiley-VCH, Weinheim.

Mann, J. (1992) *Murder, magic, and medicine*, Chapter 1. Oxford University Press, Oxford.

Page, C., Curtis, M., Sutter, M., Walker, M., and Hoffman, B. (2002) Drug names and drug classification systems. in *Integrated pharmacology 2nd edn*, Chapter 2. Mosby, Elsevier, Maryland Heights, MO.

Sneader, W. (2005) *Drug discovery: a history*. John Wiley and Sons, Chichester.

## WEBSITES

International non-proprietary names, World Health Organization. [www.who.int/medicines/services/inn/en/](http://www.who.int/medicines/services/inn/en/)

Brand names of some commonly used drugs.  
[www.mwrckmanuals.com/professional/appendices/brand-names-of-some-commonly-used-drugs?starting with=a](http://www.mwrckmanuals.com/professional/appendices/brand-names-of-some-commonly-used-drugs?starting%20with%3D%20a)

*Titles for general further reading are listed on p.845.*

# PART A

## Drug targets

Medicinal chemistry is the study of how novel drugs can be designed and developed. This process is helped immeasurably by a detailed understanding of the structure and function of the molecular targets that are present in the body.

The major drug targets are normally large molecules (macromolecules), such as proteins and nucleic acids. Knowing the structures, properties, and functions of these macromolecules is crucial if we are to design new drugs. There are a variety of reasons for this.

Firstly, it is important to know what functions different macromolecules have in the body and whether targeting them is likely to have a beneficial effect in treating a particular disease. There is no point designing a drug to inhibit a digestive enzyme if one is looking for a new analgesic.

Secondly, a knowledge of macromolecular structure is crucial if one is to design a drug that will bind effectively to the target. Knowing the target structure and its functional groups will allow the medicinal chemist to design a drug that contains complementary functional groups that will bind the drug to the target.

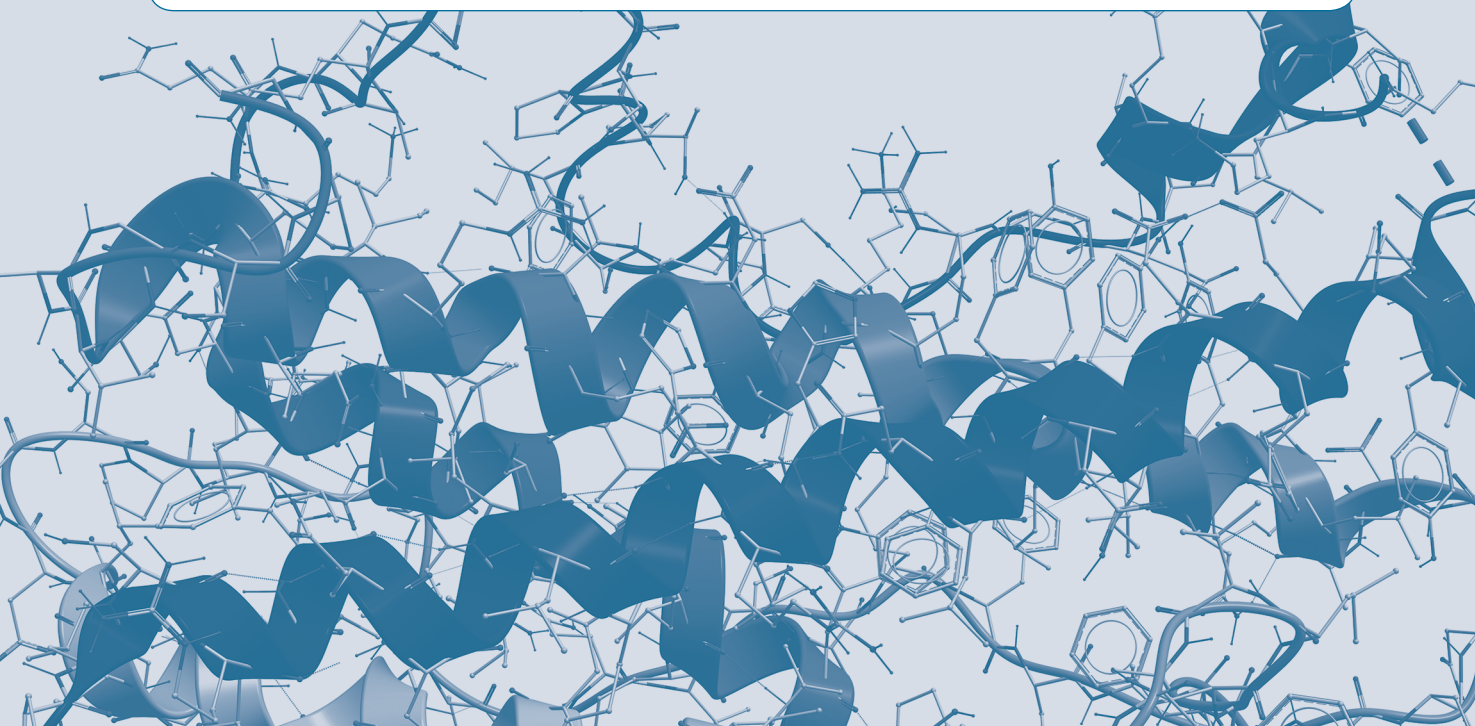
Thirdly, a drug must not only bind to the target, it must bind to the correct region of the target. Proteins and

nucleic acids are extremely large molecules in comparison to a drug and if the drug binds to the wrong part of the macromolecule, it may not have any effect. An appreciation of the target's structure and function will guide the medicinal chemist in this respect.

Finally, an understanding of how a macromolecule operates is crucial if one is going to design an effective drug that will interfere with that process. For example, understanding the mechanism of how enzymes catalyse reactions has been extremely important in the design of many important drugs, for example the protease inhibitors used in HIV therapy (section 20.7).

Proteins are the most important drug targets used in medicinal chemistry and so it should be no surprise that the major focus in Part A (Chapters 2–5) is devoted to them. However, there are some important drugs which interact with nucleic acids. The structure and function of these macromolecules are covered in Chapter 6.

If you have a background in biochemistry, much of the material in this section may already be familiar to you, and you may wish to move directly to Part B. Alternatively, you may find the material in Part A useful revision.







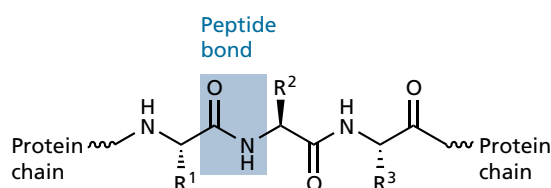
# 2

## Protein structure and function

The vast majority of drugs used in medicine are targeted on proteins such as receptors, enzymes, and transport proteins. Therefore, it is important to understand protein structure in order to understand drug action on proteins. Proteins have four levels of structure—primary, secondary, tertiary, and quaternary.

### 2.1 The primary structure of proteins

The primary structure is the order in which the individual amino acids making up the protein are linked together through peptide bonds (Fig. 2.1). The 20 common amino acids found in humans are listed in Table 2.1, with the three-letter and one-letter codes often used to represent



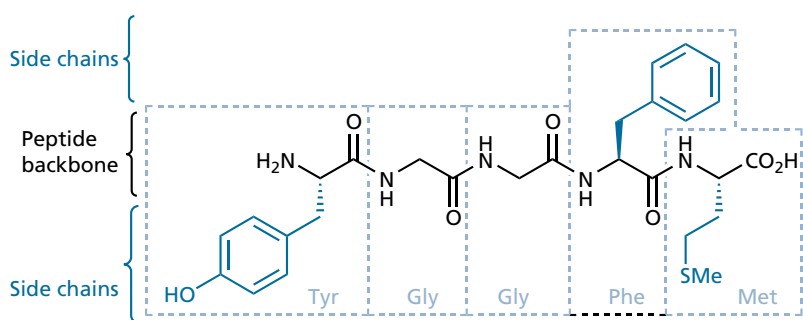
**FIGURE 2.1** Primary structure of proteins (R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> = amino acid side chains).

them. The structures of the amino acids are shown in Appendix 1. The primary structure of **Met-enkephalin** (one of the body's own painkillers) is shown in Fig. 2.2.

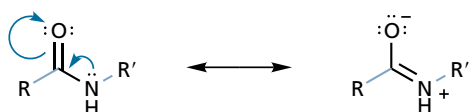
The peptide bond in proteins is planar in nature as a result of the resonance structure shown in Fig. 2.3. This gives the peptide bond a significant double bond character which prevents rotation. As a result, bond rotation in the protein backbone is only possible for the bonds on

**TABLE 2.1** The 20 common amino acids found in humans.

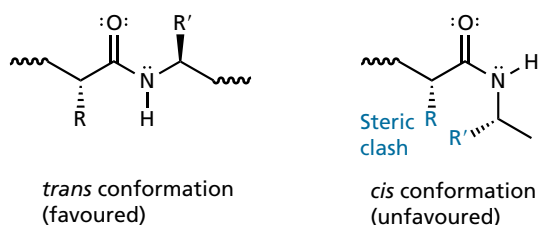
Synthesized in the human body			Essential to the diet		
Amino acid	Codes		Amino acid	Codes	
	3-letter	1-letter		3-letter	1-letter
Alanine	Ala	A	Histidine	His	H
Arginine	Arg	R	Isoleucine	Ile	I
Asparagine	Asn	N	Leucine	Leu	L
Aspartic acid	Asp	D	Lysine	Lys	K
Cysteine	Cys	C	Methionine	Met	M
Glutamic acid	Glu	E	Phenylalanine	Phe	F
Glutamine	Gln	Q	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Proline	Pro	P	Valine	Val	V
Serine	Ser	S			
Tyrosine	Tyr	Y			



**FIGURE 2.2** Met-enkephalin. The short hand notation for this peptide is H-Tyr-Gly-Gly-Phe-Met-OH or YGGFM.



**FIGURE 2.3** The planar peptide bond (free bond rotation allowed for coloured bonds only).



**FIGURE 2.4** *Trans* and *cis* conformations of the peptide bond.

either side of each peptide bond. This has an important consequence for protein tertiary structure (section 2.3.6).


There are two possible conformations for the peptide bond (Fig. 2.4). The *trans* conformation is the one that is normally present in proteins, because the *cis* conformation leads to a steric clash between the residues. However, the *cis* conformation is possible for peptide bonds next to a proline residue.

## 2.2 The secondary structure of proteins

The secondary structure of proteins consists of regions of ordered structure adopted by the protein chain. In structural proteins such as wool and silk, secondary structures are extensive and determine the overall shape and properties of such proteins. However, there are also regions of secondary structure in most other proteins. There are three main secondary structures—the  $\alpha$ -helix,  $\beta$ -pleated sheet, and  $\beta$ -turn.

### 2.2.1 The $\alpha$ -helix

The  $\alpha$ -helix results from coiling of the protein chain such that the peptide bonds making up the backbone are able to form hydrogen bonds between each other. These hydrogen bonds are directed along the axis of the helix, as shown in Fig. 2.5. The side chains of the component amino acids stick out at right angles from the helix, thus minimizing steric interactions and further stabilizing the structure. Other less common types of helices can occur in proteins, such as the 3(10)-helix which is more stretched than the ideal  $\alpha$ -helix, and the  $\pi$ -helix which is more compact and extremely rare.

 Test your understanding and practise your molecular modelling with Exercise 2.1 on the Online Resource Centre: at [www.oxfordtextbooks.co.uk/orc/patrick6e/](http://www.oxfordtextbooks.co.uk/orc/patrick6e/)

### 2.2.2 The $\beta$ -pleated sheet

The  $\beta$ -pleated sheet is a layering of protein chains one on top of another, as shown in Fig. 2.6. Here too, the structure is held together by hydrogen bonds between the peptide chains. The side chains are situated at right angles to the sheets, once again to reduce steric interactions. The chains in  $\beta$ -sheets can run in opposite directions (antiparallel) or in the same direction (parallel) (Fig. 2.7).

### 2.2.3 The $\beta$ -turn

A  $\beta$ -turn allows the polypeptide chain to turn abruptly and go in the opposite direction. This is important in allowing the protein to adopt a more globular compact shape. A hydrogen bonding interaction between the first and third peptide bond of the turn is important in stabilizing the turn (Fig. 2.8). Less abrupt changes in the direction of the polypeptide chain can also take place through longer loops, which are less regular in their structure, but are often rigid and well defined.

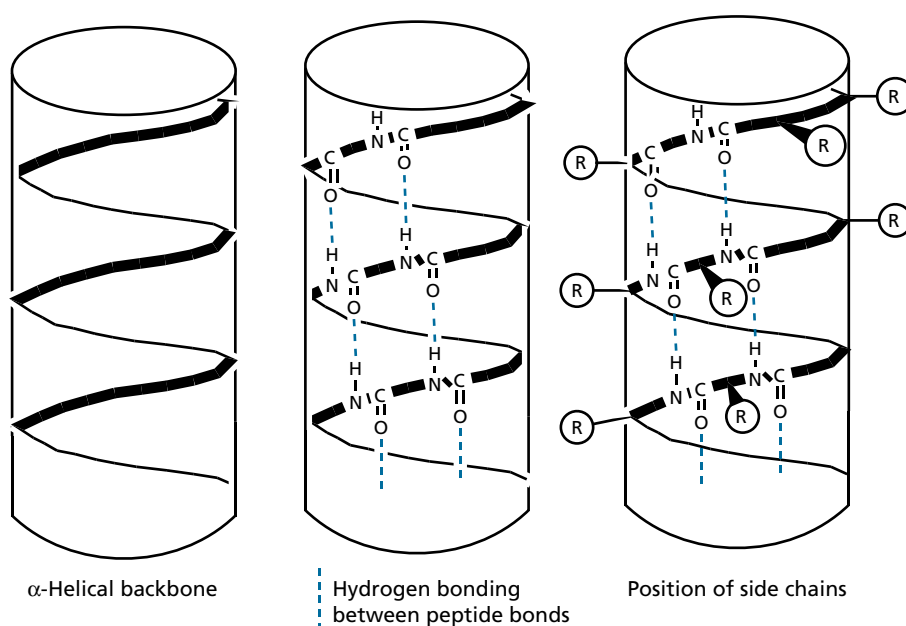


FIGURE 2.5 The  $\alpha$ -helix for proteins showing intramolecular hydrogen bonds and the position of side chains.

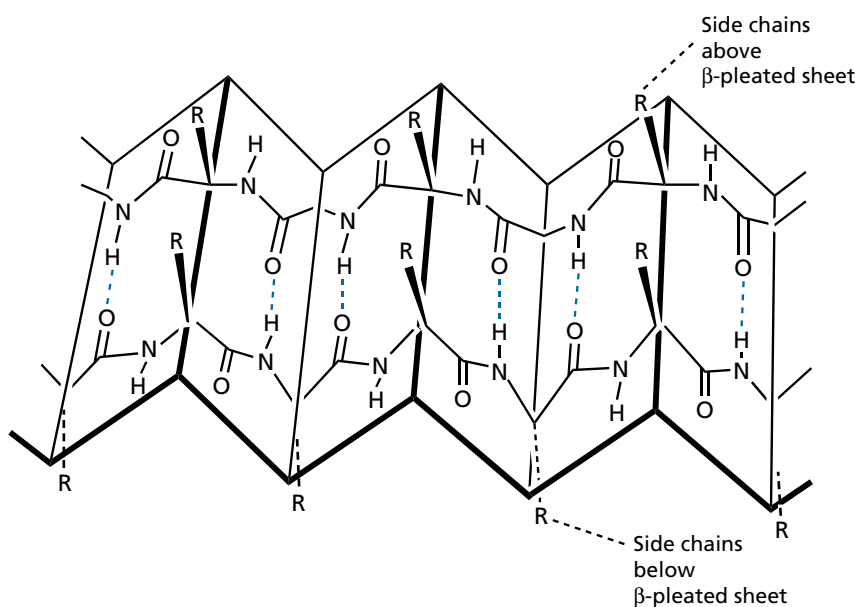


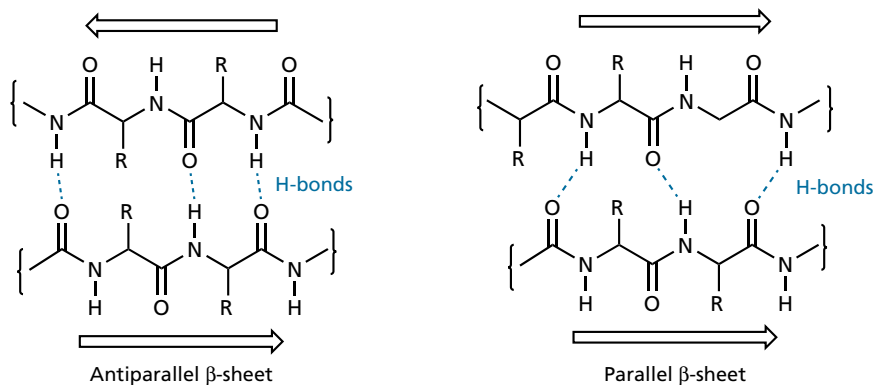
FIGURE 2.6 The  $\beta$ -pleated sheet (antiparallel arrangement).

## 2.3 The tertiary structure of proteins

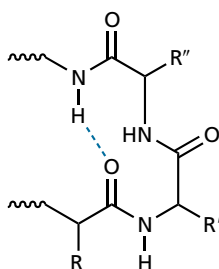
The tertiary structure is the overall three-dimensional shape of a protein. Structural proteins are quite ordered in shape, whereas globular proteins, such as enzymes and receptors (Chapters 3 and 4), fold up to form more complex structures. The tertiary structure of enzymes

and receptors is crucial to their function and also to their interaction with drugs; therefore it is important to appreciate the forces that control tertiary structure.

Globular proteins often contain regions of ordered secondary structure, the extent of which varies from protein to protein. For example, **cyclin-dependent kinase 2** (a protein that catalyses phosphorylation reactions) has several regions of  $\alpha$ -helices and  $\beta$ -pleated sheets (Fig. 2.9), whereas the digestive enzyme **chymotrypsin**



**FIGURE 2.7** Hydrogen bonding in antiparallel and parallel  $\beta$ -sheets (the arrows are pointing to the C-terminal end of the chain).



**FIGURE 2.8** The  $\beta$ -turn showing hydrogen bonding between the first and third peptide bond.

has very little secondary structure. Nevertheless, the protein chains in both cyclin-dependent kinase 2 and chymotrypsin fold up to form a complex, but distinctive, globular shape. How does this come about?

At first sight, the three-dimensional structure of cyclin-dependent kinase 2 looks like a ball of string after the cat has been at it. In fact, the structure shown is a very precise shape which is taken up by every molecule of this protein, and which is determined by the protein's primary structure<sup>1</sup>. Indeed, in the laboratory, it is possible to synthesize proteins which automatically adopt the same three-dimensional structure and function as the naturally occurring protein. The HIV-1 protease enzyme is an example (section 20.7.4.1).

This poses a problem. Why should a chain of amino acids take up such a precise three-dimensional shape? At first sight, it does not make sense. If we place a length of string on the table, it does not fold itself up into a precise complex shape. So why should a chain of amino acids do such a thing?

The answer lies in the fact that a protein is not just a bland piece of string. That is because it contains a large



**FIGURE 2.9** The pdb file (1hcl) for human cyclin-dependent kinase 2 (CDK2) where cylinders represent  $\alpha$ -helices and arrows represent  $\beta$ -sheets. A pdb file contains the 3D structural information for a protein and can be downloaded from the Brookhaven protein data bank. Each protein structure file is given a code, for example, 1hcl.

number of different chemical functional groups, which include the peptide bonds of the polypeptide backbone, as well as a variety of functional groups in the amino acid side chains. These can interact with each other, such that there is either an attractive or a repulsive interaction. Thus, the protein will twist and turn to minimize the unfavourable interactions and maximize the favourable ones until the most stable shape or conformation is found—the tertiary structure (Fig. 2.10).

With the exception of disulphide bonds, the attractive interactions involved in tertiary structure are the same as the **intermolecular bonds** described in section 1.3. The latter occur between different molecules, whereas the bonds controlling protein tertiary structure occur within

<sup>1</sup> Some proteins contain species known as **cofactors** (e.g. metal ions or small organic molecules) which also have an effect on tertiary structure.

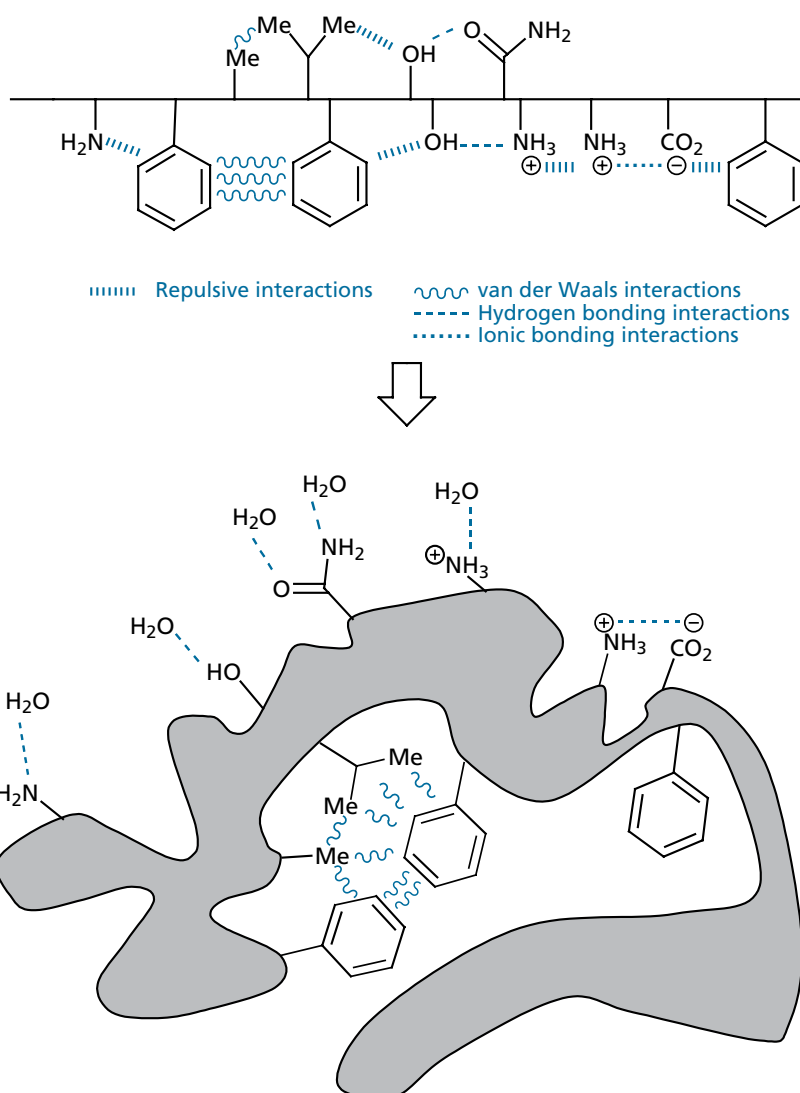



FIGURE 2.10 Tertiary structure formation as a result of intramolecular interactions.

the same molecule, and so they are called **intramolecular bonds**. Nevertheless, the principles described in section 1.3 are the same.

 Test your understanding and practise your molecular modelling with Exercise 2.2 on the Online Resource Centre: at [www.oxfordtextbooks.co.uk/orc/patrick6e/](http://www.oxfordtextbooks.co.uk/orc/patrick6e/)

### 2.3.1 Covalent bonds: disulphide links

Cysteine has a residue containing a thiol group capable of forming a covalent bond in protein tertiary structure. When two such residues are close together, a covalent disulphide bond can be formed as a result of oxidation. A covalent bridge is thus formed between two different parts of the protein chain (Fig. 2.11). It should be noted that the two cysteine residues involved in this bond

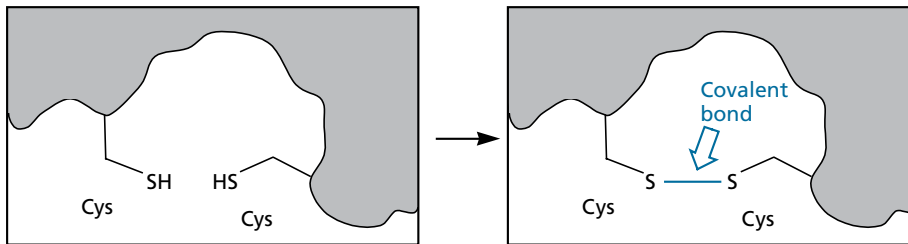
formation may be far apart from each other in the primary structure of the protein, but are brought close together as a result of protein folding.

### 2.3.2 Ionic or electrostatic bonds

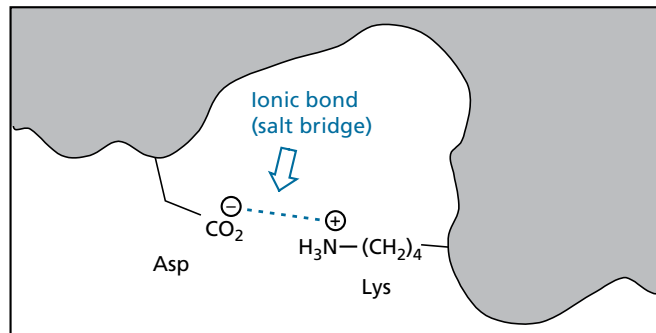
An ionic bond or salt bridge can be formed between the carboxylate ion of an acidic residue such as aspartic acid or glutamic acid, and the aminium ion of a basic residue such as lysine, arginine, or histidine (Fig. 2.12). This is the strongest of the intramolecular bonds.

### 2.3.3 Hydrogen bonds

Hydrogen bonds can be viewed as a weak form of ionic interaction as they involve interactions between atoms having partial charges. They can be formed between

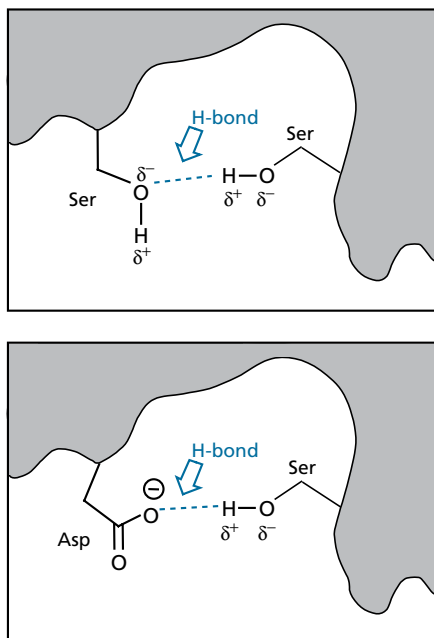


**FIGURE 2.11** The formation of a disulphide covalent bond between two cysteine side chains.



**FIGURE 2.12** Ionic bonding between an aspartate side chain and a lysine side chain.

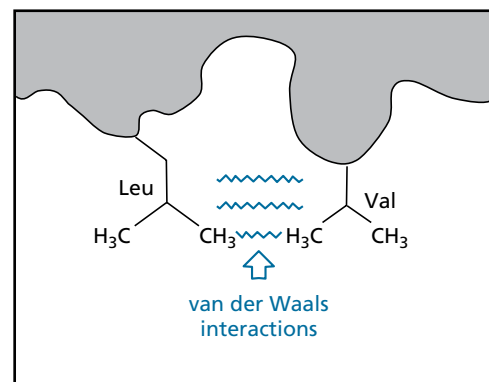
a large number of amino acid residues such as serine, threonine, aspartic acid, glutamic acid, glutamine, lysine, arginine, histidine, tryptophan, tyrosine, and asparagine. Two examples are shown in Fig. 2.13.



**FIGURE 2.13** Hydrogen bonding between amino acid side chains.

### 2.3.4 Van der Waals and hydrophobic interactions

Van der Waals interactions are weaker interactions than hydrogen bonds, and can take place between two hydrophobic regions of the protein. For example, they can take place between two alkyl groups (Fig. 2.14). The amino acids alanine, valine, leucine, isoleucine, phenylalanine, and proline all have hydrophobic side chains capable of interacting with each other by van der Waals interactions. The side chains of other amino acids such as methionine, tryptophan, threonine, and tyrosine contain polar functional groups, but the side chains also have a substantial



**FIGURE 2.14** Van der Waals interactions between amino acid side chains.