

Detailed contents

List of boxes	xxvi		
Acronyms and abbreviations	xxviii		
1 Drugs and drug targets: an overview	1		
1.1 What is a drug?	1		
1.2 Drug targets	3		
1.2.1 Cell structure	3		
1.2.2 Drug targets at the molecular level	4		
1.3 Intermolecular bonding forces	5		
1.3.1 Electrostatic or ionic bonds	5		
1.3.2 Hydrogen bonds	6		
1.3.3 Van der Waals interactions	8		
1.3.4 Dipole–dipole and ion–dipole interactions	8		
1.3.5 Repulsive interactions	9		
1.3.6 The role of water and hydrophobic interactions	10		
1.4 Pharmacokinetic issues and medicines	11		
1.5 Classification of drugs	11		
1.6 Naming of drugs and medicines	12		
PART A Drug targets			
2 Protein structure and function	17		
2.1 The primary structure of proteins	17		
2.2 The secondary structure of proteins	18		
2.2.1 The α -helix	18		
2.2.2 The β -pleated sheet	18		
2.2.3 The β -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		
3 Enzymes: structure and function	30		
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		
3.5 The catalytic role of enzymes	32		
3.5.1 Binding interactions	32		
3.5.2 Acid–base catalysis	33		
3.5.3 Nucleophilic groups	34		
3.5.4 Stabilization of the transition state	35		
3.5.5 Cofactors	35		
3.5.6 Naming and classification of enzymes	37		
3.5.7 Genetic polymorphism and enzymes	37		
3.6 Regulation of enzymes	38		
3.7 Isozymes	40		
3.8 Enzyme kinetics	41		
3.8.1 The Michaelis–Menten equation	41		
3.8.2 Lineweaver–Burk plots	42		
Box 3.1 The external control of enzymes by nitric oxide	39		
4 Receptors: structure and function	44		
4.1 Role of the receptor	44		
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		

4.9	Intracellular receptors	59
4.10	Regulation of receptor activity	59
4.11	Genetic polymorphism and receptors	60
5	Receptors and signal transduction	61
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 α -subunit	62
5.2	Signal transduction involving G-proteins and adenylate cyclase	63
5.2.1	Activation of adenylate cyclase by the α_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_β	68
5.3.1	G-protein effect on phospholipase C_β	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
6	Nucleic acids: structure and function	77
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

7	Enzymes as drug targets	93
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
8	Receptors as drug targets	109
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	11 Pharmacokinetics and related topics	162	
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
9	Nucleic acids as drug targets	128	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
10	Miscellaneous drug targets	144	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	Case study 1: Statins	187	
Box 10.1	Antidepressant drugs acting on transport proteins	145	■ CS1.1	Cholesterol and coronary heart disease	187
Box 10.2	Targeting transcription factor–coactivator interactions	149	■ CS1.2	The target enzyme	188
Box 10.3	Cyclodextrins as drug scavengers	159	■ CS1.3	The discovery of statins	190
			■ CS1.4	Mechanism of action for statins: pharmacodynamics	192
			■ CS1.5	Binding interactions of statins	192
			■ CS1.6	Other mechanisms of action for statins	193
			■ CS1.7	Other targets for cholesterol-lowering drugs	194

PART C Drug discovery, design, and development

12 Drug discovery: finding a lead	197		
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	13 Drug design: optimizing target interactions	223
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
14	Drug design: optimizing access to the target	256	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	15	Getting the drug to market	284
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	Case study 2: The design of ACE inhibitors	302	
			Box CS2.1	Synthesis of captopril and enalaprilat	307
			Case study 3: Artemisinin and related antimalarial drugs	309	
			■ 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
		17.1.3 Choice of method	350
Case study 4: The design of oxamniquine	315	17.2 Drawing chemical structures	350
■ CS4.1 Introduction	315	17.3 3D structures	350
■ CS4.2 From lucanthone to oxamniquine	315	17.4 Energy minimization	351
■ CS4.3 Mechanism of action	319	17.5 Viewing 3D molecules	351
■ CS4.4 Other agents	319	17.6 Molecular dimensions	353
Box CS4.1 Synthesis of oxamniquine	320	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
			378

PART D Tools of the trade

16 Combinatorial and parallel synthesis 325

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

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	20	Antiviral agents	490
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 β -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 β -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
21 Anticancer agents	543		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 ₃ 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		
21.6.2.10 Multi-receptor tyrosine kinase inhibitors	591		
21.6.2.11 Kinase inhibition involving protein–protein binding interactions	595		
21.6.3 Receptor antagonists of the hedgehog signalling pathway	595		
21.7 Miscellaneous enzyme inhibitors	596		
21.7.1 Matrix metalloproteinase inhibitors	596		
21.7.2 Proteasome inhibitors	597		
21.7.3 Histone deacetylase inhibitors	600		
21.7.4 Inhibitors of poly ADP ribose polymerase	602		
21.7.5 Other enzyme targets	603		
21.8 Agents affecting apoptosis	603		
21.9 Miscellaneous anticancer agents	604		
21.9.1 Synthetic agents	605		
21.9.2 Natural products	606		
21.9.3 Protein therapy	608		
21.9.4 Modulation of transcription factor–coactivator interactions	608		
21.10 Antibodies, antibody conjugates, and gene therapy	609		
21.10.1 Monoclonal antibodies	609		
21.10.2 Antibody–drug conjugates	611		
21.10.3 Antibody-directed enzyme prodrug therapy (ADEPT)	612		
21.10.4 Antibody-directed abzyme prodrug therapy (ADAPT)	614		
21.10.5 Gene-directed enzyme prodrug therapy (GDEPT)	614		
21.10.6 Other forms of gene therapy	615		
21.11 Photodynamic therapy	615		
21.12 Viral therapy	616		
Box 21.1 Clinical aspects of intercalating agents	554		
Box 21.2 Clinical aspects of non-intercalating agents inhibiting the action of topoisomerase enzymes on DNA	556		
Box 21.3 Clinical aspects of alkylating and metallating agents	559		
Box 21.4 Clinical aspects of antimetabolites	565		
Box 21.5 Clinical aspects of hormone-based therapies	571		
Box 21.6 Clinical aspects of drugs acting on structural proteins	575		
Box 21.7 General synthesis of gefitinib and related analogues	582		
Box 21.8 General synthesis of imatinib and analogues	586		
Box 21.9 Design of sorafenib	592		
Box 21.10 Clinical aspects of kinase inhibitors	593		
		22 Cholinergics, anticholinergics, and anticholinesterases	620
		22.1 The peripheral nervous system	620
		22.2 Motor nerves of the peripheral nervous system	620
		22.2.1 The somatic motor nervous system	621
		22.2.2 The autonomic motor nervous system	621
		22.2.3 The enteric system	622
		22.2.4 Defects in motor nerve transmission	622
		22.3 The cholinergic system	622
		22.3.1 The cholinergic signalling system	622
		22.3.2 Presynaptic control systems	623
		22.3.3 Cotransmitters	623
		22.4 Agonists at the cholinergic receptor	623
		22.5 Acetylcholine: structure, SAR, and receptor binding	624
		22.6 The instability of acetylcholine	626
		22.7 Design of acetylcholine analogues	627
		22.7.1 Steric shields	627
		22.7.2 Electronic effects	627
		22.7.3 Combining steric and electronic effects	628
		22.8 Clinical uses for cholinergic agonists	628
		22.8.1 Muscarinic agonists	628
		22.8.2 Nicotinic agonists	628
		22.9 Antagonists of the muscarinic cholinergic receptor	629
		22.9.1 Actions and uses of muscarinic antagonists	629
		22.9.2 Muscarinic antagonists	629
		22.9.2.1 Atropine and hyoscyne	629
		22.9.2.2 Structural analogues of atropine and hyoscyne	631
		22.9.2.3 Simplified analogues of atropine	631
		22.9.2.4 Quinuclidine muscarinic agents	633
		22.9.2.5 Other muscarinic antagonists	633
		22.10 Antagonists of the nicotinic cholinergic receptor	635
		22.10.1 Applications of nicotinic antagonists	635
		22.10.2 Nicotinic antagonists	635
		22.10.2.1 Curare and tubocurarine	635
		22.10.2.2 Decamethonium and suxamethonium	636
		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 β_1 -blockers (second-generation β -blockers)	669
22.13.1 Carbamates	642	23.11.3.4 Short-acting β -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 β -blockers	670
22.15.3 Multi-targeted agents acting on the acetylcholinesterase enzyme and the muscarinic M_2 receptor	650	24 The opioid analgesics	678
Box 22.1 Clinical applications for muscarinic antagonists	634	24.1 History of opium	678
Box 22.2 Muscarinic antagonists for the treatment of COPD	634	24.2 The active principle: morphine	678
Box 22.3 Mosses play it smart	652	24.2.1 Isolation of morphine	678
23 Drugs acting on the adrenergic nervous system	654	24.2.2 Structure and properties	679
23.1 The adrenergic nervous system	654	24.3 Structure–activity relationships	679
23.1.1 Peripheral nervous system	654	24.4 The molecular target for morphine: opioid receptors	682
23.1.2 Central nervous system	654	24.5 Morphine: pharmacodynamics and pharmacokinetics	682
23.2 Adrenergic receptors	654	24.6 Morphine analogues	684
23.2.1 Types of adrenergic receptor	654	24.6.1 Variation of substituents	684
23.2.2 Distribution of receptors	655	24.6.2 Drug extension	684
23.3 Endogenous agonists for the adrenergic receptors	656	24.6.3 Simplification or drug dissection	686
23.4 Biosynthesis of catecholamines	656	24.6.3.1 Removing ring E	686
23.5 Metabolism of catecholamines	657	24.6.3.2 Removing ring D	686
23.6 Neurotransmission	657	24.6.3.3 Removing rings C and D	687
23.6.1 The neurotransmission process	657	24.6.3.4 Removing rings B, C, and D	688
23.6.2 Cotransmitters	657	24.6.3.5 Removing rings B, C, D, and E	689
23.6.3 Presynaptic receptors and control	658	24.6.4 Rigidification	690
23.7 Drug targets	659	24.7 Agonists and antagonists	693
23.8 The adrenergic binding site	659	24.8 Endogenous opioid peptides and opioids	695
23.9 Structure–activity relationships	660	24.8.1 Endogenous opioid peptides	695
23.9.1 Important binding groups on catecholamines	660	24.8.2 Analogues of enkephalins and δ -selective opioids	696
23.9.2 Selectivity for α - versus β -adrenoceptors	661	24.8.3 Binding theories for enkephalins	697
23.10 Adrenergic agonists	662	24.8.4 Inhibitors of peptidases	699
23.10.1 General adrenergic agonists	662	24.8.5 Endogenous morphine	699
23.10.2 α_1 -, α_2 -, β_1 -, and β_3 -Agonists	662	24.9 The future	700
23.10.3 β_2 -Agonists and the treatment of asthma	663	24.9.1 The message-address concept	700
23.11 Adrenergic receptor antagonists	666	24.9.2 Receptor dimers	700
23.11.1 General α/β -blockers	666	24.9.3 Selective opioid agonists versus multi-targeted opioids	701
23.11.2 α -Blockers	666	24.9.4 Peripheral-acting opioids	701
23.11.3 β -Blockers as cardiovascular drugs	667	24.10 Case study: design of nalfurafine	701
23.11.3.1 First-generation β -blockers	667	Box 24.1 Clinical aspects of morphine	679
23.11.3.2 Structure–activity relationships of aryloxypropanolamines	668	Box 24.2 Synthesis of <i>N</i> -alkylated morphine analogues	685

Box 24.3 Opioids as antidiarrhoeal agents	690	26 Cardiovascular drugs	735
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
25 Anti-ulcer agents	705	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 ₂ 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 ^α -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 ₂ 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 ₂ antagonists with prolonged activity	724	26.8.4 Antisense drugs	756
25.2.10 Comparison of H ₁ and H ₂ antagonists	724	26.8.5 Inhibitors of transfer proteins	756
25.2.11 H ₂ receptors and H ₂ 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 ₁₂ 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	Case study 6: Steroidal anti-inflammatory agents	766
		■ CS6.1 Introduction to steroids	766
		■ CS6.2 Orally active analogues of cortisol	767
		■ CS6.3 Topical glucocorticoids as anti-inflammatory agents	768

xxiv Detailed contents

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

Case study 7: Current research into antidepressant agents	749	■ CS9.6 The development of rivoraxaban	793
■ CS7.1 Introduction	776	■ CS9.7 The development of edoxaban	794
■ CS7.2 The monoamine hypothesis	776	Case study 10: Reversible inhibitors of HCV NS3-4A protease	795
■ 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-HT₇ receptor	777	■ CS10.3 Modifications of the lead compound	796
Case study 8: The design and development of aliskiren	781	■ 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
Case study 9: Factor Xa inhibitors	788	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