

Contents

List of boxes	xix	3.4 Substrate binding at an active site	32
Acronyms and abbreviations	xxi	3.5 The catalytic role of enzymes	32
1 Drugs and drug targets: an overview	1	3.5.1 Binding interactions	32
1.1 What is a drug?	1	3.5.2 Acid/base catalysis	33
1.2 Drug targets	3	3.5.3 Nucleophilic groups	34
1.2.1 Cell structure	3	3.5.4 Cofactors	35
1.2.2 Drug targets at the molecular level	4	3.5.5 Naming and classification of enzymes	35
1.3 Intermolecular bonding forces	5	3.5.6 Genetic polymorphism and enzymes	35
1.3.1 Electrostatic or ionic bonds	5	3.6 Regulation of enzymes	36
1.3.2 Hydrogen bonds	6	3.7 Isozymes	39
1.3.3 Van der Waals interactions	8	3.8 Enzyme kinetics	39
1.3.4 Dipole-dipole and ion-dipole interactions	8	3.8.1 The Michaelis-Menton equation	39
1.3.5 Repulsive interactions	9	3.8.2 Lineweaver-Burk plots	40
1.3.6 The role of water and hydrophobic interactions	10		
1.4 Pharmacokinetic issues and medicines	11		
1.5 Classification of drugs	11	4 Receptors: structure and function	42
1.6 Naming of drugs and medicines	12	4.1 Role of the receptor	42
PART A Drug targets		4.2 Neurotransmitters and hormones	42
2 Protein structure and function	17	4.3 Receptor types and subtypes	45
2.1 The primary structure of proteins	17	4.4 Receptor activation	45
2.2 The secondary structure of proteins	18	4.5 How does the binding site change shape?	45
2.2.1 The α -helix	18	4.6 Ion channel receptors	47
2.2.2 The β -pleated sheet	18	4.6.1 General principles	47
2.2.3 The β -turn	18	4.6.2 Structure	48
2.3 The tertiary structure of proteins	19	4.6.3 Gating	49
2.3.1 Covalent bonds—disulphide links	21	4.6.4 Ligand-gated and voltage-gated ion channels	49
2.3.2 Ionic or electrostatic bonds	21	4.7 G-protein-coupled receptors	50
2.3.3 Hydrogen bonds	21	4.7.1 General principles	50
2.3.4 Van der Waals and hydrophobic interactions	22	4.7.2 Structure	51
2.3.5 Relative importance of bonding interactions	23	4.7.3 The rhodopsin-like family of G-protein-coupled receptors	51
2.3.6 Role of the planar peptide bond	23	4.7.4 Dimerization of G-coupled receptors	53
2.4 The quaternary structure of proteins	23	4.8 Kinase-linked receptors	53
2.5 Translation and post-translational modifications	25	4.8.1 General principles	53
2.6 Proteomics	26	4.8.2 Structure of tyrosine kinase receptors	54
2.7 Protein function	26	4.8.3 Activation mechanism for tyrosine kinase receptors	54
2.7.1 Structural proteins	26	4.8.4 Tyrosine kinase-linked receptors	54
2.7.2 Transport proteins	27	4.9 Intracellular receptors	55
2.7.3 Enzymes and receptors	27	4.10 Regulation of receptor activity	56
2.7.4 Miscellaneous proteins and protein–protein interactions	28	4.11 Genetic polymorphism and receptors	56
3 Enzymes: structure and function	30	5 Receptors and signal transduction	58
3.1 Enzymes as catalysts	30	5.1 Signal transduction pathways for G-protein-coupled receptors	58
3.2 How do enzymes catalyse reactions?	31	5.1.1 Interaction of the receptor-ligand complex with G-proteins	58
3.3 The active site of an enzyme	31	5.1.2 Signal transduction pathways involving the α -subunit	59
		5.2 Signal transduction involving G-proteins and adenylate cyclase	60

5.2.1 Activation of adenylate cyclase by the α_s -subunit	60	7.7.3 Enzyme inhibitors used against the body's own enzymes	95
5.2.2 Activation of protein kinase A	60	7.8 Enzyme kinetics	97
5.2.3 The G _i -protein	62	7.8.1 Lineweaver-Burk plots	97
5.2.4 General points about the signalling cascade involving cyclic AMP	62	7.8.2 Comparison of inhibitors	99
5.2.5 The role of the $\beta\gamma$ -dimer	63		
5.2.6 Phosphorylation	63	8 Receptors as drug targets	102
5.3 Signal transduction involving G-proteins and phospholipase C	63	8.1 Introduction	102
5.3.1 G-protein effect on phospholipase C	64	8.2 The design of agonists	102
5.3.2 Action of the secondary messenger: diacylglycerol	65	8.2.1 Binding groups	102
5.3.3 Action of the secondary messenger: inositol triphosphate	65	8.2.2 Position of the binding groups	104
5.3.4 Re-synthesis of phosphatidylinositol diphosphate	65	8.2.3 Size and shape	105
5.4 Signal transduction involving kinase-linked receptors	66	8.2.4 Other design strategies	105
5.4.1 Activation of signalling proteins and enzymes	66	8.2.5 Pharmacodynamics and pharmacokinetics	105
5.4.2 Small G-proteins	67	8.2.6 Examples of agonists	106
5.4.3 Activation of guanylate cyclase by kinase receptors	68	8.2.7 Allosteric modulators	106
6 Nucleic acids: structure and function	71	8.3 The design of antagonists	107
6.1 Structure of DNA	71	8.3.1 Antagonists acting at the binding site	107
6.1.1 The primary structure of DNA	71	8.3.2 Antagonists acting out with the binding site	110
6.1.2 The secondary structure of DNA	71	8.4 Partial agonists	111
6.1.3 The tertiary structure of DNA	74	8.5 Inverse agonists	112
6.1.4 Chromatins	76	8.6 Desensitization and sensitization	112
6.1.5 Genetic polymorphism and personalized medicine	76	8.7 Tolerance and dependence	114
6.2 Ribonucleic acid and protein synthesis	76	8.8 Receptor types and subtypes	114
6.2.1 Structure of RNA	76	8.9 Affinity, efficacy, and potency	116
6.2.2 Transcription and translation	77		
6.2.3 Small nuclear RNA	79	9 Nucleic acids as drug targets	120
6.3 Genetic illnesses	79	9.1 Intercalating drugs acting on DNA	120
6.4 Molecular biology and genetic engineering	81	9.2 Topoisomerase poisons: non-intercalating	121
		9.3 Alkylating and metallating agents	123
		9.3.1 Nitrogen mustards	124
		9.3.2 Nitrosoureas	124
		9.3.3 Busulfan	124
		9.3.4 Cisplatin	125
		9.3.5 Dacarbazine and procarbazine	126
		9.3.6 Mitomycin C	127
		9.4 Chain cutters	128
		9.5 Chain terminators	129
		9.6 Control of gene transcription	130
		9.7 Agents that act on RNA	131
		9.7.1 Agents that bind to ribosomes	131
		9.7.2 Antisense therapy	131
PART B Pharmacodynamics and pharmacokinetics	87	10 Miscellaneous drug targets	135
7 Enzymes as drug targets	89	10.1 Transport proteins as drug targets	135
7.1 Inhibitors acting at the active site of an enzyme	87	10.2 Structural proteins as drug targets	135
7.1.1 Reversible inhibitors	87	10.2.1 Viral structural proteins as drug targets	135
7.1.2 Irreversible inhibitors	89	10.2.2 Tubulin as a drug target	135
7.2 Inhibitors acting at allosteric binding sites	89	10.3 Biosynthetic building blocks as drug targets	138
7.3 Uncompetitive and non-competitive inhibitors	90	10.4 Biosynthetic processes as drug targets: chain terminators	139
7.4 Transition-state analogues: renin inhibitors	90	10.5 Protein-protein interactions	139
7.5 Suicide substrates	92		
7.6 Isozyme selectivity of inhibitors	93		
7.7 Medicinal uses of enzyme inhibitors	93		
7.7.1 Enzyme inhibitors used against microorganisms	93		
7.7.2 Enzyme inhibitors used against viruses	95		

xii Contents

10.6	Lipids as drug targets	143	12.2	Choosing a drug target	189
10.6.1	'Tunnelling molecules'	143	12.2.1	Drug targets	189
10.6.2	Ion carriers	146	12.2.2	Discovering drug targets	189
10.6.3	Tethers and anchors	147	12.2.3	Target specificity and selectivity between species	191
10.7	Carbohydrates as drug targets	148	12.2.4	Target specificity and selectivity within the body	191
10.7.1	Glycomics	148	12.2.5	Targeting drugs to specific organs and tissues	192
10.7.2	Antigens and antibodies	149	12.2.6	Pitfalls	192
10.7.3	Cyclodextrins	151	12.2.7	Multi-target drugs	193
11	Pharmacokinetics and related topics	153	12.3	Identifying a bioassay	195
11.1	The three phases of drug action	153	12.3.1	Choice of bioassay	195
11.2	A typical journey for an orally active drug	153	12.3.2	<i>In vitro</i> tests	195
11.3	Drug absorption	154	12.3.3	<i>In vivo</i> tests	195
11.4	Drug distribution	156	12.3.4	Test validity	196
11.4.1	Distribution around the blood supply	156	12.3.5	High-throughput screening	196
11.4.2	Distribution to tissues	156	12.3.6	Screening by nuclear magnetic resonance	197
11.4.3	Distribution to cells	156	12.3.7	Affinity screening	197
11.4.4	Other distribution factors	156	12.3.8	Surface plasmon resonance	197
11.4.5	Blood–brain barrier	156	12.3.9	Scintillation proximity assay	198
11.4.6	Placental barrier	157	12.3.10	Isothermal titration calorimetry	198
11.4.7	Drug–drug interactions	157	12.3.11	Virtual screening	198
11.5	Drug metabolism	157	12.4	Finding a lead compound	199
11.5.1	Phase I and phase II metabolism	158	12.4.1	Screening of natural products	199
11.5.2	Phase I transformations catalysed by cytochrome P450 enzymes	158	12.4.2	Medical folklore	202
11.5.3	Phase I transformations catalysed by flavin-containing monooxygenases	160	12.4.3	Screening synthetic compound 'libraries'	202
11.5.4	Phase I transformations catalysed by other enzymes	160	12.4.4	Existing drugs	203
11.5.5	Phase II transformations	160	12.4.5	Starting from the natural ligand or modulator	204
11.5.6	Metabolic stability	163	12.4.6	Combinatorial and parallel synthesis	207
11.5.7	The first pass effect	167	12.4.7	Computer-aided design of lead compounds	207
11.6	Drug excretion	167	12.4.8	Serendipity and the prepared mind	207
11.7	Drug administration	168	12.4.9	Computerized searching of structural databases	209
11.7.1	Oral administration	169	12.4.10	Fragment-based lead discovery	209
11.7.2	Absorption through mucous membranes	169	12.4.11	Properties of lead compounds	211
11.7.3	Rectal administration	169	12.5	Isolation and purification	212
11.7.4	Topical administration	169	12.6	Structure determination	212
11.7.5	Inhalation	170	12.7	Herbal medicine	212
11.7.6	Injection	170	13	Drug design: optimizing target interactions	215
11.7.7	Implants	171	13.1	Structure–activity relationships	215
11.8	Drug dosing	171	13.1.1	Binding role of alcohols and phenols	216
11.8.1	Drug half-life	172	13.1.2	Binding role of aromatic rings	217
11.8.2	Steady state concentration	172	13.1.3	Binding role of alkenes	218
11.8.3	Drug tolerance	173	13.1.4	The binding role of ketones and aldehydes	218
11.8.4	Bioavailability	173	13.1.5	Binding role of amines	218
11.9	Formulation	173	13.1.6	Binding role of amides	219
11.10	Drug delivery	174	13.1.7	Binding role of quaternary ammonium salts	221
	Case study 1: Statins	178	13.1.8	Binding role of carboxylic acids	221
			13.1.9	Binding role of esters	222
			13.1.10	Binding role of alkyl and aryl halides	222
			13.1.11	Binding role of thiols and ethers	223
			13.1.12	Binding role of other functional groups	223
			13.1.13	Binding role of alkyl groups and the carbon skeleton	223
			13.1.14	Binding role of heterocycles	223
			13.1.15	Isosteres	225

PART C Drug discovery, design, and development

12.	Drug discovery: finding a lead	189
12.1	Choosing a disease	189

13.1.16 Testing procedures	226	14.6.1 Prodrugs to improve membrane permeability	259
13.1.17 SAR in drug optimization	226	14.6.2 Prodrugs to prolong drug activity	260
13.2 Identification of a pharmacophore	227	14.6.3 Prodrugs masking drug toxicity and side effects	261
13.3 Drug optimization: strategies in drug design	228	14.6.4 Prodrugs to lower water solubility	262
13.3.1 Variation of substituents	228	14.6.5 Prodrugs to improve water solubility	262
13.3.2 Extension of the structure	231	14.6.6 Prodrugs used in the targeting of drugs	263
13.3.3 Chain extension/contraction	231	14.6.7 Prodrugs to increase chemical stability	263
13.3.4 Ring expansion/contraction	231	14.6.8 Prodrugs activated by external influence (sleeping agents)	264
13.3.5 Ring variations	233	14.7 Drug alliances	264
13.3.6 Ring fusions	234	14.7.1 'Sentry' drugs	264
13.3.7 Isosteres and bioisosteres	234	14.7.2 Localizing a drug's area of activity	265
13.3.8 Simplification of the structure	236	14.7.3 Increasing absorption	265
13.3.9 Rigidification of the structure	239	14.8 Endogenous compounds as drugs	265
13.3.10 Conformational blockers	241	14.8.1 Neurotransmitters	265
13.3.11 Structure-based drug design and molecular modelling	241	14.8.2 Natural hormones, peptides, and proteins as drugs	266
13.3.12 Drug design by NMR spectroscopy	243	14.8.3 Antibodies as drugs	267
13.3.13 The elements of luck and inspiration	243	14.9 Peptides and peptidomimetics in drug design	268
13.3.14 Designing drugs to interact with more than one target	243	14.9.1 Peptidomimetics	268
14 Drug design: optimizing access to the target	248	14.9.2 Peptide drugs	270
14.1 Optimizing hydrophilic/hydrophobic properties	248	14.10 Oligonucleotides as drugs	271
14.1.1 Masking polar functional groups to decrease polarity	249	15 Getting the drug to market	274
14.1.2 Adding or removing polar functional groups to vary polarity	249	15.1 Preclinical and clinical trials	274
14.1.3 Varying hydrophobic substituents to vary polarity	249	15.1.1 Toxicity testing	274
14.1.4 Variation of <i>N</i> -alkyl substituents to vary <i>pK_a</i>	250	15.1.2 Drug metabolism studies	276
14.1.5 Variation of aromatic substituents to vary <i>pK_a</i>	250	15.1.3 Pharmacology, formulation, and stability tests	277
14.1.6 Bioisosteres for polar groups	250	15.1.4 Clinical trials	277
14.2 Making drugs more resistant to chemical and enzymatic degradation	251	15.2 Patenting and regulatory affairs	281
14.2.1 Steric shields	251	15.2.1 Patents	281
14.2.2 Electronic effects of bioisosteres	251	15.2.2 Regulatory affairs	283
14.2.3 Steric and electronic modifications	252	15.3 Chemical and process development	285
14.2.4 Metabolic blockers	252	15.3.1 Chemical development	285
14.2.5 Removal or replacement of susceptible metabolic groups	253	15.3.2 Process development	286
14.2.6 Group shifts	253	15.3.3 Choice of drug candidate	289
14.2.7 Ring variation and ring substituents	254	15.3.4 Natural products	289
14.3 Making drugs less resistant to drug metabolism	255	■ Case study 2: The design of angiotensin-converting enzyme (ACE) inhibitors	292
14.3.1 Introducing metabolically susceptible groups	255	■ Case study 3: Artemisinin and related antimalarial drugs	299
14.3.2 Self-destruct drugs	255	■ Case study 4: The design of oxamniquine	305
14.4 Targeting drugs	256	PART D Tools of the trade	
14.4.1 Targeting tumour cells: 'search and destroy' drugs	256	16 Combinatorial and parallel synthesis	313
14.4.2 Targeting gastrointestinal infections	257	16.1 Combinatorial and parallel synthesis in medicinal chemistry projects	313
14.4.3 Targeting peripheral regions rather than the central nervous system	257	16.2 Solid phase techniques	314
14.4.4 Targeting with membrane tethers	257	16.2.1 The solid support	314
14.5 Reducing toxicity	258	16.2.2 The anchor/linker	315
14.6 Prodrugs	258	16.2.3 Examples of solid phase syntheses	317

16.3	Planning and designing a compound library	318	17.11.1 X-ray crystallography	355
16.3.1	'Spider-like' scaffolds	318	17.11.2 Structural comparison of active compounds	355
16.3.2	Designing 'drug-like' molecules	318	17.11.3 Automatic identification of pharmacophores	355
16.3.3	Synthesis of scaffolds	319	17.12 Docking procedures	356
16.3.4	Substituent variation	319	17.12.1 Manual docking	356
16.3.5	Designing compound libraries for lead optimization	319	17.12.2 Automatic docking	357
16.3.6	Computer-designed libraries	320	17.12.3 Defining the molecular surface of a binding site	357
16.4	Testing for activity	321	17.12.4 Rigid docking by shape complementarity	358
16.4.1	High-throughput screening	321	17.12.5 The use of grids in docking programs	361
16.4.2	Screening 'on bead' or 'off bead'	321	17.12.6 Rigid docking by matching hydrogen bonding groups	361
16.5	Parallel synthesis	322	17.12.7 Rigid docking of flexible ligands: the FLOG program	361
16.5.1	Solid phase extraction	323	17.12.8 Docking of flexible ligands: anchor and grow programs	362
16.5.2	The use of resins in solution phase organic synthesis (SPOS)	324	17.12.9 Docking of flexible ligands: simulated annealing and genetic algorithms	366
16.5.3	Reagents attached to solid support: catch and release	324	17.13 Automated screening of databases for lead compounds	366
16.5.4	Microwave technology	325	17.14 Protein mapping	366
16.5.5	Microfluidics in parallel synthesis	325	17.14.1 Constructing a model protein: homology modelling	367
16.6	Combinatorial synthesis	328	17.14.2 Constructing a binding site: hypothetical pseudoreceptors	368
16.6.1	The mix and split method in combinatorial synthesis	328	17.15 <i>De novo</i> drug design	370
16.6.2	Structure determination of the active compound(s)	329	17.15.1 General principles of <i>de novo</i> drug design	370
16.6.3	Dynamic combinatorial synthesis	331	17.15.2 Automated <i>de novo</i> drug design	371
17	Computers in medicinal chemistry	337	17.16 Planning compound libraries	379
17.1	Molecular and quantum mechanics	337	17.17 Database handling	379
17.1.1	Molecular mechanics	337		
17.1.2	Quantum mechanics	337		
17.1.3	Choice of method	337		
17.2	Drawing chemical structures	338		
17.3	Three-dimensional structures	338		
17.4	Energy minimization	339	18 Quantitative structure-activity relationships (QSAR)	383
17.5	Viewing 3D molecules	339	18.1 Graphs and equations	383
17.6	Molecular dimensions	341	18.2 Physicochemical properties	384
17.7	Molecular properties	341	18.2.1 Hydrophobicity	385
17.7.1	Partial charges	341	18.2.2 Electronic effects	388
17.7.2	Molecular electrostatic potentials	342	18.2.3 Steric factors	390
17.7.3	Molecular orbitals	343	18.2.4 Other physicochemical parameters	392
17.7.4	Spectroscopic transitions	343	18.3 Hansch equation	392
17.7.5	The use of grids in measuring molecular properties	344	18.4 The Craig plot	392
17.8	Conformational analysis	346	18.5 The Topliss scheme	394
17.8.1	Local and global energy minima	346	18.6 Bioisosteres	397
17.8.2	Molecular dynamics	346	18.7 The Free-Wilson approach	397
17.8.3	Stepwise bond rotation	347	18.8 Planning a QSAR study	397
17.8.4	Monte Carlo and the Metropolis method	348	18.9 Case study	398
17.8.5	Genetic and evolutionary algorithms	350	18.10 Three-dimensional QSAR	401
17.9	Structure comparisons and overlays	351	18.10.1 Defining steric and electrostatic fields	401
17.10	Identifying the active conformation	352	18.10.2 Relating shape and electronic distribution to biological activity	402
17.10.1	X-ray crystallography	352	18.10.3 Advantages of CoMFA over traditional QSAR	403
17.10.2	Comparison of rigid and non-rigid ligands	353		
17.11	3D pharmacophore identification	354		

xiv Contents

16.3	Planning and designing a compound library	318	17.11.1	X-ray crystallography	355
16.3.1	'Spider-like' scaffolds	318	17.11.2	Structural comparison of active compounds	355
16.3.2	Designing 'drug-like' molecules	318	17.11.3	Automatic identification of pharmacophores	355
16.3.3	Synthesis of scaffolds	319	17.12	Docking procedures	356
16.3.4	Substituent variation	319	17.12.1	Manual docking	356
16.3.5	Designing compound libraries for lead optimization	319	17.12.2	Automatic docking	357
16.3.6	Computer-designed libraries	320	17.12.3	Defining the molecular surface of a binding site	357
16.4	Testing for activity	321	17.12.4	Rigid docking by shape complementarity	358
16.4.1	High-throughput screening	321	17.12.5	The use of grids in docking programs	361
16.4.2	Screening 'on bead' or 'off bead'	321	17.12.6	Rigid docking by matching hydrogen bonding groups	361
16.5	Parallel synthesis	322	17.12.7	Rigid docking of flexible ligands: the FLOG program	361
16.5.1	Solid phase extraction	323	17.12.8	Docking of flexible ligands: anchor and grow programs	362
16.5.2	The use of resins in solution phase organic synthesis (SPOS)	324	17.12.9	Docking of flexible ligands: simulated annealing and genetic algorithms	366
16.5.3	Reagents attached to solid support: catch and release	324	17.13	Automated screening of databases for lead compounds	366
16.5.4	Microwave technology	325	17.14	Protein mapping	366
16.5.5	Microfluidics in parallel synthesis	325	17.14.1	Constructing a model protein: homology modelling	367
16.6	Combinatorial synthesis	328	17.14.2	Constructing a binding site: hypothetical pseudoreceptors	368
16.6.1	The mix and split method in combinatorial synthesis	328	17.15	<i>De novo</i> drug design	370
16.6.2	Structure determination of the active compound(s)	329	17.15.1	General principles of <i>de novo</i> drug design	370
16.6.3	Dynamic combinatorial synthesis	331	17.15.2	Automated <i>de novo</i> drug design	371
17	Computers in medicinal chemistry	337	17.16	Planning compound libraries	379
17.1	Molecular and quantum mechanics	337	17.17	Database handling	379
17.1.1	Molecular mechanics	337	18	Quantitative structure-activity relationships (QSAR)	383
17.1.2	Quantum mechanics	337	18.1	Graphs and equations	383
17.1.3	Choice of method	338	18.2	Physicochemical properties	384
17.2	Drawing chemical structures	338	18.2.1	Hydrophobicity	385
17.3	Three-dimensional structures	338	18.2.2	Electronic effects	388
17.4	Energy minimization	339	18.2.3	Steric factors	390
17.5	Viewing 3D molecules	339	18.2.4	Other physicochemical parameters	392
17.6	Molecular dimensions	341	18.3	Hansch equation	392
17.7	Molecular properties	341	18.4	The Craig plot	392
17.7.1	Partial charges	341	18.5	The Topliss scheme	394
17.7.2	Molecular electrostatic potentials	342	18.6	Bioisosteres	397
17.7.3	Molecular orbitals	343	18.7	The Free-Wilson approach	397
17.7.4	Spectroscopic transitions	343	18.8	Planning a QSAR study	397
17.7.5	The use of grids in measuring molecular properties	344	18.9	Case study	398
17.8	Conformational analysis	346	18.10	Three-dimensional QSAR	401
17.8.1	Local and global energy minima	346	18.10.1	Defining steric and electrostatic fields	401
17.8.2	Molecular dynamics	346	18.10.2	Relating shape and electronic distribution to biological activity	402
17.8.3	Stepwise bond rotation	347	18.10.3	Advantages of CoMFA over traditional QSAR	403
17.8.4	Monte Carlo and the Metropolis method	348			
17.8.5	Genetic and evolutionary algorithms	350			
17.9	Structure comparisons and overlays	351			
17.10	Identifying the active conformation	352			
17.10.1	X-ray crystallography	352			
17.10.2	Comparison of rigid and non-rigid ligands	353			
17.11	3D pharmacophore identification	354			

18.10.4 Potential problems of CoMFA	403	20 Antiviral agents	468
18.10.5 Other 3D QSAR methods	404	20.1 Viruses and viral diseases	468
18.10.6 Case study: inhibitors of tubulin polymerization	404	20.2 Structure of viruses	468
Case study 5: Design of a thymidylate synthase inhibitor	407	20.3 Life cycle of viruses	469
		20.4 Vaccination	470
		20.5 Antiviral drugs: general principles	471
		20.6 Antiviral drugs used against DNA viruses	472
		20.6.1 Inhibitors of viral DNA polymerase	472
		20.6.2 Inhibitors of tubulin polymerization	474
		20.6.3 Antisense therapy	475
PART E Selected topics in medicinal chemistry	413	20.7 Antiviral drugs acting against RNA viruses: HIV	476
19 Antibacterial agents	413	20.7.1 Structure and life cycle of HIV	476
19.1 History of antibacterial agents	415	20.7.2 Antiviral therapy against HIV	477
19.2 The bacterial cell	415	20.7.3 Inhibitors of viral reverse transcriptase	478
19.3 Mechanisms of antibacterial action	416	20.7.4 Protease inhibitors	480
19.4 Antibacterial agents which act against cell metabolism (antimetabolites)	416	20.7.5 Inhibitors of other targets	493
19.4.1 Sulphonamides	420	20.8 Antiviral drugs acting against RNA viruses: flu virus	496
19.4.2 Examples of other antimetabolites		20.8.1 Structure and life cycle of the influenza virus	496
19.5 Antibacterial agents which inhibit cell wall synthesis		20.8.2 Ion channel disrupters: adamantanes	498
19.5.1 Penicillins	421	20.8.3 Neuraminidase inhibitors	498
19.5.2 Cephalosporins	421	20.9 Antiviral drugs acting against RNA viruses: cold virus	507
19.5.3 Other β -lactam antibiotics	436	20.10 Antiviral drugs acting against RNA viruses: hepatitis C	508
19.5.4 β -Lactamase inhibitors	442	20.11 Broad-spectrum antiviral agents	510
19.5.5 Other drugs which act on bacterial cell wall biosynthesis	444	20.11.1 Agents acting against cytidine triphosphate synthetase	510
19.6 Antibacterial agents which act on the plasma membrane structure	445	20.11.2 Agents acting against S-adenosylhomocysteine hydrolase	510
19.6.1 Valinomycin and gramicidin A	450	20.11.3 Ribavirin	510
19.6.2 Polymyxin B	450	20.11.4 Interferons	510
19.6.3 Killer nanotubes	450	20.11.5 Antibodies and ribozymes	511
19.6.4 Cyclic lipopeptides	451	20.12 Bioterrorism and smallpox	511
19.7 Antibacterial agents which impair protein synthesis: translation	452		
19.7.1 Aminoglycosides	452	21 Anticancer agents	514
19.7.2 Tetracyclines	454	21.1 Cancer: an introduction	514
19.7.3 Chloramphenicol	455	21.1.1 Definitions	514
19.7.4 Macrolides	455	21.1.2 Causes of cancer	514
19.7.5 Lincosamides	456	21.1.3 Genetic faults leading to cancer: proto-oncogenes and oncogenes	514
19.7.6 Streptogramins	456	21.1.4 Abnormal signalling pathways	515
19.7.7 Oxazolidinones	457	21.1.5 Insensitivity to growth-inhibitory signals	516
19.8 Agents that act on nucleic acid transcription and replication	457	21.1.6 Abnormalities in cell cycle regulation	516
19.8.1 Quinolones and fluoroquinolones	457	21.1.7 Apoptosis and the p53 protein	517
19.8.2 Aminoacridines	459	21.1.8 Telomeres	519
19.8.3 Rifamycins	460	21.1.9 Angiogenesis	519
19.8.4 Nitroimidazoles and nitrofurantoin	460	21.1.10 Tissue invasion and metastasis	521
19.8.5 Inhibitors of bacterial RNA polymerase	461	21.1.11 Treatment of cancer	521
19.9 Miscellaneous agents	461	21.1.12 Resistance	523
19.10 Drug resistance	462	21.2 Drugs acting directly on nucleic acids	524
19.10.1 Drug resistance by mutation	462		
19.10.2 Drug resistance by genetic transfer	463		
19.10.3 Other factors affecting drug resistance	463		
19.10.4 The way ahead	463		

21.2.1	Intercalating agents	524	22	Cholinergics, anticholinergics, and anticholinesterases	578
21.2.2	Non-intercalating agents which inhibit the action of topoisomerase enzymes on DNA	526	22.1	The peripheral nervous system	578
21.2.3	Alkylating and metallating agents	526	22.2	Motor nerves of the PNS	578
21.2.4	Chain cutters	529	22.2.1	The somatic motor nervous system	579
21.2.5	Antisense therapy	529	22.2.2	The autonomic motor nervous system	579
21.3	Drugs acting on enzymes: antimetabolites	531	22.2.3	The enteric system	580
21.3.1	Dihydrofolate reductase inhibitors	531	22.2.4	Defects in motor nerve transmission	580
21.3.2	Inhibitors of thymidylate synthase	532	22.3	The cholinergic system	580
21.3.3	Inhibitors of ribonucleotide reductase	534	22.3.1	The cholinergic signalling system	580
21.3.4	Inhibitors of adenosine deaminase	535	22.3.2	Presynaptic control systems	580
21.3.5	Inhibitors of DNA polymerases	535	22.3.3	Co-transmitters	581
21.3.6	Purine antagonists	536	22.4	Agonists at the cholinergic receptor	582
21.3.7	Inhibitors of poly ADP ribose polymerase	536	22.5	Acetylcholine: structure, structure-activity relationships, and receptor binding	583
21.4	Hormone-based therapies	536	22.6	The instability of acetylcholine	584
21.4.1	Glucocorticoids, estrogens, progestins, and androgens	537	22.7	Design of acetylcholine analogues	585
21.4.2	Luteinizing hormone-releasing hormone agonists	537	22.7.1	Steric shields	585
21.4.3	Anti-estrogens	538	22.7.2	Electronic effects	586
21.4.4	Anti-androgens	538	22.7.3	Combining steric and electronic effects	586
21.4.5	Aromatase inhibitors	538	22.8	Clinical uses for cholinergic agonists	586
21.5	Drugs acting on structural proteins	539	22.8.1	Muscarinic agonists	586
21.5.1	Agents which inhibit tubulin polymerization	540	22.8.2	Nicotinic agonists	586
21.5.2	Agents which inhibit tubulin depolymerization	542	22.9	Antagonists of the muscarinic cholinergic receptor	587
21.6	Inhibitors of signalling pathways	544	22.9.1	Actions and uses of muscarinic antagonists	587
21.6.1	Inhibition of farnesyl transferase and the Ras protein	544	22.9.2	Muscarinic antagonists	588
21.6.2	Protein kinase inhibitors	547	22.10	Antagonists of the nicotinic cholinergic receptor	590
21.7	Miscellaneous enzyme inhibitors	561	22.10.1	Applications of nicotinic antagonists	590
21.7.1	Matrix metalloproteinase inhibitors	561	22.10.2	Nicotinic antagonists	591
21.7.2	Proteasome inhibitors	563	22.11	Receptor structures	594
21.7.3	Histone deacetylase inhibitors	564	22.12	Anticholinesterases and acetylcholinesterase	595
21.7.4	Other enzyme targets	564	22.12.1	Effect of anticholinesterases	595
21.8	Miscellaneous anticancer agents	564	22.12.2	Structure of the acetylcholinesterase enzyme	595
21.8.1	Synthetic agents	565	22.12.3	The active site of acetylcholinesterase	596
21.8.2	Natural products	566	22.13	Anticholinesterase drugs	597
21.8.3	Protein therapy	566	22.13.1	Carbamates	598
21.8.4	Modulation of transcription factor-co-activator interactions	567	22.13.2	Organophosphorus compounds	600
21.9	Antibodies, antibody conjugates, and gene therapy	568	22.14	Pralidoxime: an organophosphate antidote	602
21.9.1	Monoclonal antibodies	568	22.15	Anticholinesterases as 'smart drugs'	603
21.9.2	Antibody-drug conjugates	568	22.15.1	Acetylcholinesterase inhibitors	603
21.9.3	Antibody-directed enzyme prodrug therapy (ADEPT)	570	22.15.2	Dual-action agents acting on the acetylcholinesterase enzyme	604
21.9.4	Antibody-directed abzyme prodrug therapy (ADAPT)	572	22.15.3	Multi-targeted agents acting on the acetylcholinesterase enzyme and the muscarinic M ₂ receptor	606
21.9.5	Gene-directed enzyme prodrug therapy (GDEPT)	572	23	Drugs acting on the adrenergic nervous system	609
21.9.6	Other forms of gene therapy	573	23.1	The adrenergic nervous system	609
21.10	Photodynamic therapy	573			

23.1.1 Peripheral nervous system	609	24.7 Agonists and antagonists	647
23.1.2 Central nervous system	609	24.8 Endogenous opioid peptides and opioids	649
23.2 Adrenergic receptors	609	24.8.1 Endogenous opioid peptides	649
23.2.1 Types of adrenergic receptor	609	24.8.2 Analogues of enkephalins and δ -selective opioids	650
23.2.2 Distribution of receptors	610	24.8.3 Binding theories for enkephalins	652
23.3 Endogenous agonists for the adrenergic receptors	611	24.8.4 Inhibitors of peptidases	653
23.4 Biosynthesis of catecholamines	611	24.8.5 Endogenous morphine	653
23.5 Metabolism of catecholamines	612	24.9 The future	653
23.6 Neurotransmission	612	24.9.1 The message–address concept	653
23.6.1 The neurotransmission process	612	24.9.2 Receptor dimers	654
23.6.2 Co-transmitters	612	24.9.3 Selective opioid agonists versus multi-targeted opioids	655
23.6.3 Presynaptic receptors and control	613	24.9.4 Peripheral-acting opioids	655
23.7 Drug targets	614	24.10 Case study: design of nalfurafine	655
23.8 The adrenergic binding site	614	25 Anti-ulcer agents	659
23.9 Structure–activity relationships	615	25.1 Peptic ulcers	659
23.9.1 Important binding groups on catecholamines	615	25.1.1 Definition	659
23.9.2 Selectivity for α - versus β -adrenoceptors	616	25.1.2 Causes	659
23.10 Adrenergic agonists	616	25.1.3 Treatment	659
23.10.1 General adrenergic agonists	616	25.1.4 Gastric acid release	659
23.10.2 α_1 -, α_2 -, β_1 -, and β_3 -Agonists	617	25.2 H_2 antagonists	660
23.10.3 β_2 -Agonists and the treatment of asthma	618	25.2.1 Histamine and histamine receptors	661
23.11 Adrenergic receptor antagonists	620	25.2.2 Searching for a lead	662
23.11.1 General α -/ β -blockers	620	25.2.3 Developing the lead: a chelation bonding theory	665
23.11.2 α -Blockers	620	25.2.4 From partial agonist to antagonist: the development of burimamide	665
23.11.3 β -Blockers as cardiovascular drugs	621	25.2.5 Development of metiamide	667
23.12 Other drugs affecting adrenergic transmission	626	25.2.6 Development of cimetidine	670
23.12.1 Drugs that affect the biosynthesis of adrenergics	626	25.2.7 Cimetidine	671
23.12.2 Drugs inhibiting the uptake of noradrenaline into storage vesicles	627	25.2.8 Further studies of cimetidine analogues	673
23.12.3 Release of noradrenaline from storage vesicles	627	25.2.9 Further H_2 antagonists	676
23.12.4 Reuptake inhibitors of noradrenaline into presynaptic neurons	627	25.2.10 Comparison of H_1 and H_2 antagonists	678
23.12.5 Inhibition of metabolic enzymes	629	25.2.11 H_2 -receptors and H_2 antagonists	679
24 The opioid analgesics	632	25.3 Proton pump inhibitors	679
24.1 History of opium	632	25.3.1 Parietal cells and the proton pump	679
24.2 The active principle: morphine	632	25.3.2 Proton pump inhibitors	680
24.2.1 Isolation of morphine	633	25.3.3 Mechanism of inhibition	681
24.2.2 Structure and properties	633	25.3.4 Metabolism of proton pump inhibitors	682
24.3 Structure–activity relationships	633	25.3.5 Design of omeprazole and esomeprazole	682
24.4 The molecular target for morphine: opioid receptors	635	25.3.6 Other proton pump inhibitors	684
24.5 Morphine: pharmacodynamics and pharmacokinetics	636	25.4 <i>Helicobacter pylori</i> and the use of antibacterial agents	685
24.6 Morphine analogues	638	25.4.1 Discovery of <i>Helicobacter pylori</i>	685
24.6.1 Variation of substituents	638	25.4.2 Treatment	685
24.6.2 Drug extension	638	25.5 Traditional and herbal medicines	687
24.6.3 Simplification or drug dissection	640	Case study 6: Steroidal anti-inflammatory agents	689
24.6.4 Rigidification	644	Case Study 7: Current research into antidepressant agents	700
		APPENDIX 1 Essential amino acids	705
		APPENDIX 2 The standard genetic code	706

