Brief contents

List of boxes	
Acronyms and abbreviations	

1 Drugs and drug targets: an overview

PART A Drug targets

- 2 Protein structure and function
- 3 Enzymes: structure and function
- 4 Receptors: structure and function
- 5 Receptors and signal transduction
- 6 Nucleic acids: structure and function

PART B Pharmacodynamics and pharmacokinetics

	Case study 1: Statins	178
11	Pharmacokinetics and related topics	153
10	Miscellaneous drug targets	135
9	Nucleic acids as drug targets	120
8	Receptors as drug targets	102
7	Enzymes as drug targets	87

PART C Drug discovery, design, and development

12	Drug discovery: finding a lead	189
13	Drug design: optimizing target interactions	215
14	Drug design: optimizing access to the target	248
15	Getting the drug to market	274
	Case study 2: The design of angiotensin- converting enzyme (ACE) inhibitors	292
1	, , ,	292
	converting enzyme (ACE) inhibitors	292 299

PART D Tools of the trade

xix xxi

1

17

30

42

58

71

	Combinatorial and parallel synthesis Computers in medicinal chemistry	313 337
18	Quantitative structure–activity relationships (QSAR)	383
	Case study 5: Design of a thymidylate synthase inhibitor	407

PART E Selected topics in medicinal chemistry

19	Antibacterial agents	413
20	Antiviral agents	468
21	Anticancer agents	514
22	Cholinergics, anticholinergics, and	
	anticholinesterases	578
23	Drugs acting on the adrenergic	
	nervous system	609
24	The opioid analgesics	632
25	Anti-ulcer agents	659
	Case study 6: Steroidal anti-inflammatory agents	689
	Case Study 7: Current research into	
	antidepressant agents	700

	Appendix 1 Essential amino acids	705
	Appendix 2 The standard genetic code	706
	Appendix 3 Statistical data for quantitative	
)	structure-activity relationships (QSAR)	707
	Appendix 4 The action of nerves	711
, ,	Appendix 5 Microorganisms	715
)	Appendix 6 Drugs and their trade names	717
-	Appendix 7 Trade names and drugs	722
	Appendix 8 Hydrogen bonding interactions	728
2	Appendix 9 Drug properties	730
	Glossary	741
)	General further reading	761
;	Index	763

Contents

List of boxes Acronyms and abbreviations			xix xxi	
1	Drugs	s 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	Intern	nolecular 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	Pharn	nacokinetic issues and medicines	11	
1.5	5 Classification of drugs			
1.6	Naming of drugs and medicines			

PART A Drug targets

2	Prote	in structure and function	17	
2.1	The p	The primary structure of proteins		
2.2	The secondary structure of proteins			
	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 te	ertiary structure of proteins	19	
	2.3.1	Covalent bonds—disulphide links	21	
	2.3.2	Ionic or electrostatic bonds	21	
	2.3.3	7	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			
2.5	Transl	ation and post-translational modifications	25	
2.6	Protec	omics	26	
2.7	Protei	n 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	Enzyr	nes: structure and function	30	
3.1	Enzym	nes as catalysts	30	
3.2	How c	lo enzymes catalyse reactions?	31	
3.3	The a	ctive site of an enzyme	31	

3.4	Subst	rate binding at an active site	32
3.5	The ca	atalytic 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		35
	3.5.5		35
	3.5.6	Genetic polymorphism and enzymes	35
	-	ation of enzymes	36
3.7	Isozyn	nes	39
3.8	Enzym	ne kinetics	39
	3.8.1	The Michaelis-Menton equation	39
	3.8.2	Lineweaver-Burk plots	40
4	Rece	ptors: structure and function	42
4.1	Role c	of the receptor	42
4.2	Neuro	transmitters and hormones	42
4.3	Recep	otor types and subtypes	45
4.4	Recep	otor activation	45
4.5	How d	loes the binding site change shape?	45
4.6	lon ch	nannel receptors	47
	4.6.1	General principles	47
	4.6.2	Structure	48
	4.6.3	Gating	49
	4.6.4	Ligand-gated and voltage-gated ion channels	49
4.7	G-prot	tein-coupled receptors	50
	4.7.1	General principles	50
	4.7.2	Structure	51
	4.7.3	The rhodopsin-like family of	- 1
	4.7.4	G-protein-coupled receptors	51 53
4.8		Dimerization of G-coupled receptors	53
4.0	4.8.1	e-linked receptors	53
	4.8.1 4.8.2	General principles Structure of tyrosine kinase receptors	53 54
	4.8.3	Activation mechanism for tyrosine kinase	54
	1.0.0	receptors	54
	4.8.4	Tyrosine kinase-linked receptors	54
4.9	Intrac	ellular receptors	55
4.10	Regul	ation of receptor activity	56
4.11	Genet	ic polymorphism and receptors	56
5	Rece	ptors and signal transduction	58
5.1		I transduction pathways for	
		tein-coupled receptors	58
	5.1.1	Interaction of the receptor–ligand complex	
		with G-proteins	58
	5.1.2	Signal transduction pathways involving	
_		the α-subunit	59
5.2		I transduction involving G-proteins and	~~
	adeny	late cyclase	60

Contents xi

	5.2.1	Activation of adenylate cyclase by the	
		α_s -subunit	60
	5.2.2	Activation of protein kinase A	60
	5.2.3	The G _i -protein	62
	5.2.4	General points about the signalling cascade	
		involving cyclic AMP	62
	5.2.5	The role of the $\beta\gamma$ -dimer	63
	5.2.6	Phosphorylation	63
5.3	-	I transduction involving G-proteins and	
	phosp	holipase C	64
	5.3.1	G-protein effect on phospholipase C	64
	5.3.2	Action of the secondary messenger:	
		diacylglycerol	65
	5.3.3	Action of the secondary messenger: inositol	
		triphosphate	65
	5.3.4	Re-synthesis of phosphatidylinositol	65
- 4	0.	diphosphate	05
5.4	-	I transduction involving kinase-linked	~ ~
	recept		66
	5.4.1	Activation of signalling proteins and enzymes	66
	5.4.2	Small G-proteins	67
	5.4.3	Activation of guanylate cyclase by kinase	68
		receptors	00
6	Nucle	eic acids: structure and function	71
6.1	Struct	ure of DNA	71
	6.1.1	The primary structure of DNA	71
	6.1.2	The secondary structure of DNA	71
	6.1.3	The tertiary structure of DNA	74
	6.1.4	Chromatins	76
	6.1.5	Genetic polymorphism and personalized	
		medicine	76
6.2	Ribon	ucleic acid and protein synthesis	76
	6.2.1	Structure of RNA	76
	6.2.2	Transcription and translation	77
	6.2.3	Small nuclear RNA	79
6.3	Genet	ic illnesses	79
6.4	Molec	ular biology and genetic engineering	81
5.4	moree	and should and genetic engineering	01

PART B Pharmacodynamics and pharmacokinetics

7	Enzyr	nes as drug targets	87		
7.1	Inhibi	tors acting at the active site of an enzyme	87		
	7.1.1	Reversible inhibitors	87		
	7.1.2	Irreversible inhibitors	89		
7.2	Inhibi	tors acting at allosteric binding sites	89		
7.3	Uncompetitive and non-competitive inhibitors				
7.4	Transition-state analogues: renin inhibitors				
7.5	Suicide substrates 9				
7.6	Isozyme selectivity of inhibitors				
7.7	Medicinal uses of enzyme inhibitors				
	7.7.1	Enzyme inhibitors used against			
		microorganisms	93		
	7.7.2	Enzyme inhibitors used against viruses	95		

		95
7.0	own enzymes	
7.8	Enzyme kinetics	97
	7.8.1 Lineweaver-Burk plots	97
	7.8.2 Comparison of inhibitors	99
8	Receptors as drug targets	102
8.1	Introduction	102
8.2	The design of agonists	102
	8.2.1 Binding groups	102
	8.2.2 Position of the binding groups	104
	8.2.3 Size and shape	105
	8.2.4 Other design strategies	105
	8.2.5 Pharmacodynamics and pharmacokinetics8.2.6 Examples of agonists	105 106
	8.2.7 Allosteric modulators	100
8.3	The design of antagonists	107
0.0	8.3.1 Antagonists acting at the binding site	107
	8.3.2 Antagonists acting out with the	
	binding site	110
8.4	8	111
8.5	Inverse agonists	112
8.6	Desensitization and sensitization	112
8.7	Tolerance and dependence	114
8.8	Receptor types and subtypes	114
8.9	Affinity, efficacy, and potency	116
9	Nucleic acids as drug targets	120
	Intercalating drugs acting on DNA	120
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
10	Miscellaneous drug targets	135
	Transport proteins as drug targets	135
	Structural proteins as drug targets	135
	10.2.1 Viral structural proteins as drug targets	135
	10.2.2 Tubulin as a drug target	135
10.3	Biosynthetic building blocks as drug targets	138
10.4	Biosynthetic processes as drug targets: chain	
	terminators	139
10.5	Protein-protein interactions	139

7.7.3 Enzyme inhibitors used against the body's

xii Contents

10.6	Lipids	as drug targets	143
	10.6.1	'Tunnelling molecules'	143
	10.6.2	Ion carriers	146
	10.6.3	Tethers and anchors	147
10.7	Carboł	nydrates as drug targets	148
	10.7.1	Glycomics	148
	10.7.2	Antigens and antibodies	149
	10.7.3	Cyclodextrins	151
11	Pharm	acokinetics and related topics	153
11.1	The th	ree phases of drug action	153
11.2	A typic	cal journey for an orally active drug	153
11.3	Drug a	bsorption	154
11.4		listribution	156
	11.4.1		156
	11.4.2		156
	11.4.3		156
	11.4.4		156
	11.4.5	Blood-brain barrier	156
	11.4.6	Placental barrier	157
	11.4.7	Drug-drug interactions	157
11.5	Drug n	netabolism	157
	11.5.1	Phase I and phase II metabolism	158
	11.5.2	Phase I transformations catalysed by	
		cytochrome P450 enzymes	158
	11.5.3	Phase I transformations catalysed by	
		flavin-containing monooxygenases	160
	11.5.4	Phase I transformations catalysed by	1.60
	1155	other enzymes Phase II transformations	160
	11.5.5 11.5.6		160 163
	11.5.7	The first pass effect	165
11.6		xcretion	167
11.7		dministration	168
		Oral administration	169
	11.7.2	1 0	169
	11.7.3 11.7.4		169 169
	11.7.4	Topical administration Inhalation	109
	11.7.6	Injection	170
	11.7.7	Implants	171
11.8	Drug d		171
11.0	11.8.1		172
	11.8.2	Steady state concentration	172
	11.8.3	Drug tolerance	173
	11.8.4	Bioavailability	173
11.9	Formu	•	173
11.10	Drug d	lelivery	174
		study 1: Statins	178

PART C Drug discovery, design, and development

12. Drug discovery: finding a lead 189

12.1 Choosing a disease

12.2	Choosi	ng a drug target	189
	12.2.1	Drug targets	189
	12.2.2	Discovering drug targets	189
	12.2.3	Target specificity and selectivity between species	191
	12.2.4	*	
		the body	191
	12.2.5	Targeting drugs to specific organs	
		and tissues	192
	12.2.6		192
		Multi-target drugs	193
12.3		ying a bioassay	195
		Choice of bioassay	195
	12.3.2		195
		<i>In vivo</i> tests Test validity	195 196
	12.3.4		190
	12.3.6		190
		Affinity screening	197
		Surface plasmon resonance	197
	12.3.9		198
	12.3.10	Isothermal titration calorimetry	198
	12.3.11	Virtual screening	198
12.4	Finding	g a lead compound	199
	12.4.1	Screening of natural products	199
	12.4.2	Medical folklore	202
	12.4.3	Screening synthetic compound 'libraries'	202
	12.4.4	Existing drugs	203
	12.4.5	Starting from the natural ligand or modulator	204
	12.4.6	Combinatorial and parallel synthesis	207
		Computer-aided design of lead compounds	207
	12.4.8		207
	12.4.9		209
	12410	Fragment-based lead discovery	209
		Properties of lead compounds	211
12 5		on and purification	212
		ure determination	212
12.7	Herbal	medicine	212
	-	lesign: optimizing target interactions	215
13.1	Structu	ure-activity relationships	215
	13.1.1	Binding role of alcohols and phenols	216
	13.1.2	Binding role of aromatic rings	217
	13.1.3	Binding role of alkenes	218
	13.1.4	The binding role of ketones and aldehydes	218
	13.1.5	Binding role of amines	218
	13.1.6 13.1.7	0	219 221
	13.1.8		221
	13.1.9		221
		Binding role of alkyl and aryl halides	222
		Binding role of thiols and ethers	223
		Binding role of other functional groups	223
	13.1.13	Binding role of alkyl groups and the carbon skeleton	223
	13114	Binding role of heterocycles	223
		Isosteres	225

	13.1.16	Testing procedures	226
	13.1.17	SAR in drug optimization	226
13.2	Identif	ication of a pharmacophore	227
13.3	Drug o	ptimization: strategies in drug design	228
	13.3.1	Variation of substituents	228
	13.3.2	Extension of the structure	231
	13.3.3	Chain extension/contraction	231
	13.3.4	Ring expansion/contraction	231
		Ring variations	233
		Ring fusions	234
		Isosteres and bioisosteres	234
		Simplification of the structure	236
		Rigidification of the structure	239
		Conformational blockers	241
	13.3.11	Structure-based drug design and molecular	241
	12212	modelling	241 243
		Drug design by NMR spectroscopy The elements of luck and inspiration	245 243
		Designing drugs to interact with more	243
	15.5.14	than one target	243
			210
	_		
14	-	lesign: optimizing access to	
	the tai	rget	248
14.1	Optimi	zing hydrophilic/hydrophobic properties	248
	14.1.1	Masking polar functional groups to	
		decrease polarity	249
	14.1.2	Adding or removing polar functional	2.40
	1412	groups to vary polarity	249
	14.1.3	Varying hydrophobic substituents to vary polarity	249
	1414	Variation of <i>N</i> -alkyl substituents to	249
	14.1.4	variation of N -arkyl substituents to vary pK_a	250
	14.1.5	Variation of aromatic substituents to	
		vary pK	250
	14.1.6	Bioisosteres for polar groups	250
14.2	Making	g drugs more resistant to chemical and	
	enzyma	atic degradation	251
		Steric shields	251
	14.2.2	Electronic effects of bioisosteres	251
	14.2.3	Steric and electronic modifications	252
	14.2.4	Metabolic blockers	252
	14.2.5	Removal or replacement of susceptible	
		metabolic groups	253
	14.2.6	1	253
	14.2.7	Ring variation and ring substituents	254
14.3	Making	g drugs less resistant to drug metabolism	255
	14.3.1	Introducing metabolically susceptible	
		groups	255
		Self-destruct drugs	255
14.4	-	ng drugs	256
	14.4.1	Targeting tumour cells: 'search and destroy'	254
	1440	drugs	256
		Targeting gastrointestinal infections	257
	14.4.3	Targeting peripheral regions rather than the central nervous system	257
	14.4.4	Targeting with membrane tethers	257
14 5		ing toxicity	258
14.0	Prodru	go	258

	14.6.1	Prodrugs to improve membrane permeability	259
	14.6.2	Prodrugs to prolong drug activity	260
	14.6.3	Prodrugs masking drug toxicity and	200
		side effects	261
	14.6.4	Prodrugs to lower water solubility	262
	14.6.5	Prodrugs to improve water solubility	262
	14.6.6	Prodrugs used in the targeting of drugs	263
	14.6.7	Prodrugs to increase chemical stability	263
	14.6.8	Prodrugs activated by external influence (sleeping agents)	264
14.7	Drug a	lliances	264
	14.7.1	'Sentry' drugs	264
	14.7.2	Localizing a drug's area of activity	265
	14.7.3	Increasing absorption	265
14.8	Endog	enous compounds as drugs	265
	14.8.1	Neurotransmitters	265
	14.8.2		
		as drugs	266
	14.8.3	Antibodies as drugs	267
14.9	Peptid	es and peptidomimetics in drug design	268
	14.9.1	Peptidomimetics	268
	14.9.2	Peptide drugs	270
14.10	Oligon	ucleotides as drugs	271
15	Gettin	g the drug to market	274
15 15.1		g the drug to market nical and clinical trials	274 274
	Preclin	nical and clinical trials Toxicity testing Drug metabolism studies	274
	Preclir 15.1.1	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and	274 274 276
	Preclir 15.1.1 15.1.2 15.1.3	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests	274 274 276 277
15.1	Preclir 15.1.1 15.1.2 15.1.3 15.1.4	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials	274 274 276 277 277
	Preclin 15.1.1 15.1.2 15.1.3 15.1.4 Patent	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs	274 274 276 277 277 281
15.1	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents	274 274 276 277 277 281 281
15.1 15.2	Preclin 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs	274 274 276 277 277 281 281 283
15.1	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemic	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development	274 274 276 277 277 281 281 283 285
15.1 15.2	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development	274 274 276 277 277 281 281 283 285 285
15.1 15.2	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development	274 274 276 277 277 281 281 283 285 285 285 286
15.1 15.2	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate	274 274 276 277 277 281 281 283 285 285
15.1 15.2	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2 15.3.3 15.3.4	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate Natural products	274 274 276 277 281 281 283 285 285 285 286 289
15.1 15.2	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2 15.3.3 15.3.4 Case s	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate Natural products tudy 2: The design of angiotensin-	274 274 276 277 281 281 283 285 285 285 286 289 289
15.115.215.3	Precir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2 15.3.3 15.3.4 Case s conver	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate Natural products tudy 2: The design of angiotensin- ting enzyme (ACE) inhibitors	274 274 276 277 281 281 283 285 285 285 286 289
15.1 15.2	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2 15.3.3 15.3.4 Case s Conver Case s	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate Natural products tudy 2: The design of angiotensin- ting enzyme (ACE) inhibitors tudy 3: Artemisinin and related	274 274 276 277 281 281 283 285 285 285 285 286 289 289 289
15.1 15.2 15.3	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2 15.3.3 15.3.4 Case s conver Case s antima	hical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate Natural products tudy 2: The design of angiotensin- ting enzyme (ACE) inhibitors tudy 3: Artemisinin and related Marial drugs	274 274 276 277 281 281 283 285 285 285 286 289 289
15.1 15.2 15.3	Preclir 15.1.1 15.1.2 15.1.3 15.1.4 Patent 15.2.1 15.2.2 Chemin 15.3.1 15.3.2 15.3.3 15.3.4 Case s conver Case s antima	nical and clinical trials Toxicity testing Drug metabolism studies Pharmacology, formulation, and stability tests Clinical trials ing and regulatory affairs Patents Regulatory affairs cal and process development Chemical development Process development Choice of drug candidate Natural products tudy 2: The design of angiotensin- ting enzyme (ACE) inhibitors tudy 3: Artemisinin and related	274 274 276 277 281 281 283 285 285 285 285 286 289 289 289

PART D Tools of the trade

16	Combinatorial and parallel synthesis	313
16.1	Combinatorial and parallel synthesis	
	in medicinal chemistry projects	313
16.2	Solid phase techniques	
	16.2.1 The solid support	314
	16.2.2 The anchor/linker	315
	16.2.3 Examples of solid phase syntheses	317

xiv Contents

16.3	Plannir	ng and designing a compound library	318
	16.3.1	'Spider-like' scaffolds	318
	16.3.2	Designing 'drug-like' molecules	318
	16.3.3	Synthesis of scaffolds	319
	16.3.4	Substituent variation	319
	16.3.5	Designing compound libraries for lead	
	1626	optimization	319
	16.3.6	Computer-designed libraries	320
16.4	-	for activity	321
	16.4.1	High-throughput screening	321
	16.4.2	Screening 'on bead' or 'off bead'	321
16.5		l synthesis	322
	16.5.1	Solid phase extraction	323
	16.5.2	The use of resins in solution phase organic	
	1652	synthesis (SPOS)	324
	16.5.3	Reagents attached to solid support: catch and release	324
	16.5.4	Microwave technology	325
	16.5.5	Microfluidics in parallel synthesis	325
16.6		natorial synthesis	328
10.0	16.6.1	The mix and split method in combinatorial	520
	10.0.1	synthesis	328
	16.6.2	Structure determination of the active	
		compound(s)	329
	16.6.3	Dynamic combinatorial synthesis	331
17	Compu	iters in medicinal chemistry	337
17.1	Molecu	lar and quantum mechanics	337
	17.1.1	Molecular mechanics	337
	17.1.1 17.1.2	Quantum mechanics	337 337
17.2	17.1.2 17.1.3	Quantum mechanics	337
17.2 17.3	17.1.2 17.1.3 Drawing	Quantum mechanics Choice of method	337 338
	17.1.2 17.1.3 Drawing Three-c	Quantum mechanics Choice of method g chemical structures dimensional structures	337 338 338
17.3	17.1.2 17.1.3 Drawing Three-c Energy	Quantum mechanics Choice of method g chemical structures dimensional structures minimization	337 338 338 338
17.3 17.4 17.5	17.1.2 17.1.3 Drawing Three-c Energy Viewing	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules	337 338 338 338 338 339 339
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-or Energy Viewing Molecu	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules ilar dimensions	337 338 338 338 338 339 339 341
17.3 17.4 17.5	17.1.2 17.1.3 Drawing Three-c Energy Viewing Molecu	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules llar dimensions llar properties	337 338 338 338 338 339 339 341 341
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-c Energy Viewing Molecu 17.7.1	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules lar dimensions lar properties Partial charges	337 338 338 338 339 339 341 341 341
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-oc Energy Viewing Molecu 17.7.1 17.7.2	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules tlar dimensions tlar properties Partial charges Molecular electrostatic potentials	337 338 338 338 339 339 341 341 341 342
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu 17.7.1 17.7.2 17.7.3	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals	337 338 338 338 339 339 341 341 341 342 343
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu 17.7.1 17.7.2 17.7.3 17.7.4	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions	337 338 338 338 339 339 341 341 341 342
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu 17.7.1 17.7.2 17.7.3	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals	337 338 338 338 339 339 341 341 341 342 343
17.3 17.4 17.5 17.6	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties	337 338 338 339 339 341 341 341 342 343 343
17.3 17.4 17.5 17.6 17.7	17.1.2 17.1.3 Drawing Three-c Energy Viewing Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules lar dimensions lar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis	337 338 338 339 339 341 341 341 342 343 343 343
17.3 17.4 17.5 17.6 17.7	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima	337 338 338 339 339 341 341 341 342 343 343 343 344 346
17.3 17.4 17.5 17.6 17.7	17.1.2 17.1.3 Drawin; Three-oc Energy Viewing Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules lar dimensions lar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis	337 338 338 339 339 341 341 341 342 343 343 343 344 346 346 346
17.3 17.4 17.5 17.6 17.7	17.1.2 17.1.3 Drawin; Three-oc Energy Viewin; Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1 17.8.2	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima Molecular dynamics	337 338 338 339 341 341 341 342 343 343 343 344 346 346 346 346
17.3 17.4 17.5 17.6 17.7	17.1.2 17.1.3 Drawin; Three-oc Energy Viewin; Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1 17.8.2 17.8.3	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima Molecular dynamics Stepwise bond rotation	337 338 338 339 339 341 341 341 342 343 343 343 344 346 346 346 346 347
17.3 17.4 17.5 17.6 17.7	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1 17.8.2 17.8.3 17.8.4 17.8.5	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima Molecular dynamics Stepwise bond rotation Monte Carlo and the Metropolis method	337 338 338 339 341 341 341 342 343 343 343 344 346 346 346 346 347 348
17.3 17.4 17.5 17.6 17.7 17.8	17.1.2 17.1.3 Drawing Three-C Energy Viewing Molecu Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1 17.8.2 17.8.3 17.8.4 17.8.5 Structu	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima Molecular dynamics Stepwise bond rotation Monte Carlo and the Metropolis method Genetic and evolutionary algorithms	337 338 338 339 339 341 341 341 342 343 343 343 344 346 346 346 346 347 348 350
17.3 17.4 17.5 17.6 17.7 17.8	17.1.2 17.1.3 Drawing Three-oc Energy Viewing Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1 17.8.2 17.8.3 17.8.4 17.8.5 Structu Identify	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima Molecular dynamics Stepwise bond rotation Monte Carlo and the Metropolis method Genetic and evolutionary algorithms are comparisons and overlays	337 338 338 339 341 341 341 342 343 343 344 346 346 346 346 346 346 346
17.3 17.4 17.5 17.6 17.7 17.8	17.1.2 17.1.3 Drawing Three-oc Energy Viewing Molecu Molecu 17.7.1 17.7.2 17.7.3 17.7.4 17.7.5 Conforr 17.8.1 17.8.2 17.8.3 17.8.4 17.8.5 Structu Identify 17.10.1	Quantum mechanics Choice of method g chemical structures dimensional structures minimization g 3D molecules dar dimensions dar properties Partial charges Molecular electrostatic potentials Molecular orbitals Spectroscopic transitions The use of grids in measuring molecular properties mational analysis Local and global energy minima Molecular dynamics Stepwise bond rotation Monte Carlo and the Metropolis method Genetic and evolutionary algorithms are comparisons and overlays ing the active conformation	337 338 338 339 341 341 341 342 343 343 344 346 346 346 346 346 346 346

	17.11.1	X-ray crystallography	355
	17.11.2	Structural comparison of active	
		compounds	355
	17.11.3	Automatic identification of	
		pharmacophores	355
17.12	Dockin	g procedures	356
	17.12.1	Manual docking	356
	17.12.2	Automatic docking	357
	17.12.3	Defining the molecular surface of	
		a binding site	357
		Rigid docking by shape complementarity	358
		The use of grids in docking programs	361
	17.12.6	Rigid docking by matching hydrogen bonding groups	361
	17.12.7	Rigid docking of flexible ligands: the FLOG program	361
	17.12.8	Docking of flexible ligands: anchor and grow programs	362
	17.12.9	Docking of flexible ligands: simulated annealing and genetic algorithms	366
17.13	Automa	ated screening of databases for lead	
	compo	unds	366
17.14	Protein	mapping	366
		Constructing a model protein: homology modelling	367
	17.14.2	Constructing a binding site: hypothetical	
		pseudoreceptors	368
17.15	De nov	<i>o</i> drug design	370
		General principles of <i>de novo</i> drug design	370
		Automated <i>de novo</i> drug design	371
17.16	Plannir	ng compound libraries	379
17.17	Databa	se handling	379
18	Quanti	tative structure-activity	
		nships (QSAR)	383
18.1		and equations	383
18.2	•	ochemical properties	384
10.7	ETIVSIC(.204

18.1	Graphs	and equations	383
18.2	Physico	ochemical properties	384
	18.2.1	Hydrophobicity	385
	18.2.2	Electronic effects	388
	18.2.3	Steric factors	390
	18.2.4	Other physicochemical parameters	392
18.3	Hansch	n equation	392
18.4	The Cra	aig plot	392
18.5	The Top	pliss scheme	394
18.6	Bioisos	teres	397
18.7	The Fre	ee-Wilson approach	397
18.8	Plannir	ng a QSAR study	397
18.9	Case st	udy	398
18.10	Three-o	dimensional QSAR	401
	18.10.1	Defining steric and electrostatic fields	401
	18.10.2	Relating shape and electronic distribution	
		to biological activity	402
	18.10.3	Advantages of CoMFA over traditional QSAR	403
		QUAI	403

18.10.4 Potential problems of CoMFA	403
18.10.5 Other 3D QSAR methods	404
18.10.6 Case study: inhibitors of tubulin	
polymerization	404
Case study 5: Design of a thymidylate synthase	
inhibitor	407

PART E Selected topics in medicinal chemistry

19	Antiba	cterial agents	413
19.1	History	of antibacterial agents	413
19.2	The ba	cterial cell	415
19.3	Mechai	nisms of antibacterial action	415
19.4	Antibad	cterial agents which act against cell	
	metabo	olism (antimetabolites)	416
	19.4.1	Sulphonamides	416
	19.4.2	Examples of other antimetabolites	420
19.5	Antibad	cterial agents which inhibit cell	
	wall sy	nthesis	421
	19.5.1	Penicillins	421
	19.5.2	Cephalosporins	436
	19.5.3	Other β -lactam antibiotics	442
		β-Lactamase inhibitors	444
	19.5.5	Other drugs which act on bacterial cell wall biosynthesis	445
19.6	Antibad	•	115
19.0		cterial agents which act on the plasma ane structure	450
	19.6.1	Valinomycin and gramicidin A	450
	19.6.2	Polymyxin B	450
	19.6.3	Killer nanotubes	450
	19.6.4	Cyclic lipopeptides	451
19.7	Antibad	cterial agents which impair protein	
		sis: translation	452
	19.7.1	Aminoglycosides	452
	19.7.2	Tetracyclines	454
	19.7.3	Chloramphenicol	455
	19.7.4	Macrolides	455
	19.7.5	Lincosamides	456
	19.7.6	1 0	456
	19.7.7		456
19.8		that act on nucleic acid transcription	
		olication	457
	19.8.1		457
	19.8.2	Aminoacridines	459
		Rifamycins	460
	19.8.4 19.8.5	Nitroimidazoles and nitrofurantoin	460
10.0		Inhibitors of bacterial RNA polymerase	461
19.9		aneous agents	461
19.10	Drug re	esistance	462
		Drug resistance by mutation	462
		Drug resistance by genetic transfer	463
		Other factors affecting drug resistance	463
	19.10.4	The way ahead	463

20	Antivir	al agents	468
20.1	Viruses	and viral diseases	468
20.2	Structu	ure of viruses	468
20.3	Life cy	cle of viruses	469
20.4	Vaccina	ation	470
20.5	Antivira	al drugs: general principles	471
20.6	Antivira	al 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
20.7	Antivira	al drugs acting against RNA	
	viruses	: HIV	476
	20.7.1		476
	20.7.2	17 0	477
		Inhibitors of viral reverse transcriptase	478
		Protease inhibitors	480
00.0	20.7.5	Inhibitors of other targets	493
20.8		al drugs acting against RNA viruses:	100
	flu viru		496
	20.8.1	Structure and life cycle of the influenza virus	496
	20.8.2	Ion channel disrupters: adamantanes	498
	20.8.3	Neuraminidase inhibitors	498
20.9	Antivira	al drugs acting against RNA viruses:	
	cold vii		507
20.10		al drugs acting against RNA viruses:	
	hepatit		508
20.11		spectrum antiviral agents	510
	20.11.1	Agents acting against cytidine	
	20.11.2	triphosphate synthetase	510
	20.11.2	Agents acting against S-adenosylhomocysteine hydrolase	510
	20.11.3	Ribavirin	510
		Interferons	510
	20.11.5	Antibodies and ribozymes	511
20.12	Bioterr	orism and smallpox	511
21	Antica	ncer agents	514
21.1	Cancer	: an introduction	514

~1.1	ouncer		514
	21.1.1	Definitions	514
	21.1.2	Causes of cancer	514
	21.1.3	Genetic faults leading to cancer: proto-	
		oncogenes and oncogenes	514
	21.1.4	Abnormal signalling pathways	515
	21.1.5	Insensitivity to growth-inhibitory	
		signals	516
	21.1.6	Abnormalities in cell cycle regulation	516
	21.1.7	Apoptosis and the p53 protein	517
	21.1.8	Telomeres	519
	21.1.9	Angiogenesis	519
	21.1.10	Tissue invasion and metastasis	521
	21.1.11	Treatment of cancer	521
	21.1.12	Resistance	523
21.2	Drugs a	acting directly on nucleic acids	524

xvi Contents

	21.2.1	Intercalating agents	524
	21.2.2	Non-intercalating agents which	
		inhibit the action of topoisomerase	
		enzymes on DNA	526
	21.2.3	Alkylating and metallating agents	526
	21.2.4	Chain cutters	529
	21.2.5	Antisense therapy	529
21.3	Drugs	acting on enzymes: antimetabolites	531
	21.3.1	Dihydrofolate reductase inhibitors	531
	21.3.2	Inhibitors of thymidylate synthase	532
	21.3.3	Inhibitors of ribonucleotide	
		reductase	534
	21.3.4		535
	21.3.5		535
	21.3.6	8	536
	21.3.7	Inhibitors of poly ADP ribose	
		polymerase	536
21.4	Hormo	one-based therapies	536
	21.4.1	,,	
		progestins, and androgens	537
	21.4.2	Luteinizing hormone-releasing hormone	
		agonists	537
	21.4.3	8	538
	21.4.4	0	538
	21.4.5	Aromatase inhibitors	538
21.5	Drugs	acting on structural proteins	539
	21.5.1	Agents which inhibit tubulin	
		polymerization	540
	21.5.2	Agents which inhibit tubulin	5.40
		depolymerization	542
21.6	Inhibit	tors of signalling pathways	544
	21.6.1		
		and the Ras protein	544
	21.6.2	Protein kinase inhibitors	547
21.7	Miscel	laneous enzyme inhibitors	561
	21.7.1	Matrix metalloproteinase	
		inhibitors	561
	21.7.2		563
	21.7.3		564
		Other enzyme targets	564
21.8	Miscel	laneous anticancer agents	564
	21.8.1	Synthetic agents	565
	21.8.2	Natural products	566
	21.8.3	17	566
	21.8.4	Modulation of transcription	
		factor-co-activator interactions	567
21.9	Antibo	dies, antibody conjugates,	
	and gene therapy		
	21.9.1	Monoclonal antibodies	568
	21.9.2	Antibody-drug conjugates	568
	21.9.3	Antibody-directed enzyme prodrug	
		therapy (ADEPT)	570
	21.9.4	Antibody-directed abzyme prodrug	
		therapy (ADAPT)	572
	21.9.5	Gene-directed enzyme prodrug	
		therapy (GDEPT)	572
	21.9.6	Other forms of gene therapy	573
21.10	Photoc	dynamic therapy	573

22 Cholinergics, anticholinergics, and anticholinesterases

		anticholinesterases	578	
	22.1	The peripheral nervous system		
	22.2	Motor nerves of the PNS	578	
		22.2.1 The somatic motor nervous system	579	
		22.2.2 The autonomic motor nervous system	579	
		22.2.3 The enteric system	580	
		22.2.4 Defects in motor nerve transmission	580	
	22.3	The cholinergic system	580	
		22.3.1 The cholinergic signalling system22.3.2 Presynaptic control systems	580 580	
		22.3.2 Co-transmitters	580	
	22.4	Agonists at the cholinergic receptor	582	
	22.5			
		relationships, and receptor binding	583	
	22.6	.6 The instability of acetylcholine		
	22.7	Design of acetylcholine analogues	585	
		22.7.1 Steric shields	585	
		22.7.2 Electronic effects	586	
		22.7.3 Combining steric and electronic effects	586	
	22.8	Clinical uses for cholinergic agonists	586	
		22.8.1 Muscarinic agonists	586	
	22.0	22.8.2 Nicotinic agonists	586	
	22.9	Antagonists of the muscarinic cholinergic receptor	587	
		22.9.1 Actions and uses of muscarinic	567	
		antagonists	587	
		22.9.2 Muscarinic antagonists	588	
	22.10	Antagonists of the nicotinic cholinergic		
		receptor	590	
		22.10.1 Applications of nicotinic antagonists	590	
		22.10.2 Nicotinic antagonists	591	
		Receptor structures	594	
	22.12	Anticholinesterases and acetylcholinesterase	595	
		22.12.1 Effect of anticholinesterases	595	
		22.12.2 Structure of the acetylcholinesterase enzyme	595	
		22.12.3 The active site of acetylcholinesterase	596	
	22.13	Anticholinesterase drugs	597	
		22.13.1 Carbamates	598	
		22.13.2 Organophosphorus compounds	600	
	22.14	Pralidoxime: an organophosphate		
		antidote	602	
	22.15	Anticholinesterases as 'smart drugs'	603	
		22.15.1 Acetylcholinesterase inhibitors	603	
		22.15.2 Dual-action agents acting on the	604	
		acetylcholinesterase enzyme 22.15.3 Multi-targeted agents acting on the	004	
		acetylcholinesterase enzyme and the		
		muscarinic M_2 receptor	606	
	23	Drugs acting on the adrenergic		
23		nervous system		
	23.1	The adrenergic nervous system	609 609	

23.1 The adrenergic nervous system

Contents xvii

	23.1.1 23.1.2	Peripheral nervous system Central nervous system	609 609
02.0			
23.2		rgic receptors	609
	23.2.1 23.2.2	Types of adrenergic receptor	609 610
<u></u>		Distribution of receptors	010
23.3	-	enous agonists for the adrenergic	611
	recepto		611
23.4	-	thesis of catecholamines	611
23.5	Metabolism of catecholamines		612
23.6	Neurot	ransmission	612
	23.6.1	The neurotransmission process	612
	23.6.2		612
	23.6.3	Presynaptic receptors and control	613
23.7	Drug targets		614
23.8	The ad	renergic binding site	614
23.9	Structu	re-activity relationships	615
	23.9.1	Important binding groups on	
		catecholamines	615
	23.9.2	Selectivity for α - versus	(1)
00.10		β-adrenoceptors	616
23.10		rgic agonists	616
		General adrenergic agonists	616 617
		α_1 -, α_2 -, β_1 -, and β_3 -Agonists β_2 -Agonists and the treatment of asthma	618
22 11		rgic receptor antagonists	620
23.11		General α -/ β -blockers	620
		α-Blockers	620
		β-Blockers as cardiovascular drugs	621
23.12		drugs affecting adrenergic transmission	626
		Drugs that affect the biosynthesis	
		of adrenergics	626
	23.12.2	Drugs inhibiting the uptake of noradrenaline into storage vesicles	627
	23 12 3	Release of noradrenaline from storage	027
	20.12.0	vesicles	627
	23.12.4	Reuptake inhibitors of noradrenaline	
		into presynaptic neurons	627
	23.12.5	Inhibition of metabolic enzymes	629
24	The op	bioid analgesics	632
24.1	History	of opium	632
24.2	The act	tive principle: morphine	632
	24.2.1	Isolation of morphine	632
	24.2.2	Structure and properties	633
24.3	Structu	ire-activity relationships	633
24.4	The mo	plecular target for morphine:	
		receptors	635
24.5	Morphine: pharmacodynamics and		
21.0			636
24.6	pharmacokinetics 24.6 Morphine analogues		638
24.0	24.6.1	Variation of substituents	638
	24.6.1	Drug extension	638
	24.6.3	Simplification or drug dissection	640
	24.6.4	Rigidification	644

2	24.7	Agonis	ts and antagonists	647
24.8		Endogenous opioid peptides and opioids		
		24.8.1	Endogenous opioid peptides	649
		24.8.2	Analogues of enkephalins and	
			δ-selective opioids	650
		24.8.3	Binding theories for enkephalins	652
		24.8.4 24.8.5	Inhibitors of peptidases	653 653
~	10		Endogenous morphine	
2	24.9	The fut		653
		24.9.1 24.9.2	The message-address concept Receptor dimers	653 654
		24.9.2	Selective opioid agonists versus	034
		21.9.3	multi-targeted opioids	655
		24.9.4	Peripheral-acting opioids	655
2	24.10	Case st	tudy: design of nalfurafine	655
	25	Anti-u	Icer agents	659
2	25.1	Peptic	-	659
-	.0.1	25.1.1	Definition	659
		25.1.2		659
			Treatment	659
		25.1.4	Gastric acid release	659
2	25.2	H_2 anta	agonists	660
		25.2.1	Histamine and histamine receptors	661
		25.2.2	Searching for a lead	662
		25.2.3	Developing the lead: a chelation	665
		25.2.4	bonding theory From partial agonist to antagonist: the	005
		23.2.1	development of burimamide	665
		25.2.5	Development of metiamide	667
		25.2.6	Development of cimetidine	670
		25.2.7	Cimetidine	671
		25.2.8	Further studies of cimetidine analogues	673
		25.2.9	Further H_2 antagonists	676
			Comparison of H_1 and H_2 antagonists H_2 -receptors and H_2 antagonists	678 679
~		25.2.11		
2	25.3		pump inhibitors	679
		25.3.1 25.3.2	Parietal cells and the proton pump Proton pump inhibitors	679 680
		25.3.2	Mechanism of inhibition	681
		25.3.4	Metabolism of proton pump inhibitors	682
		25.3.5	Design of omeprazole and esomeprazole	682
		25.3.6	Other proton pump inhibitors	684
2	25.4	Helicot	<i>bacter pylori</i> and the use of	
		antibac	terial agents	685
		25.4.1	Discovery of Helicobacter pylori	685
		25.4.2	Treatment	685
2	25.5	Traditio	onal and herbal medicines	687
		Case st	tudy 6: Steroidal anti-inflammatory	
		agents		689
		Case Study 7: Current research into		
		antidep	pressant agents	700
Д	PPFN	IDIX 1 F	ssential amino acids	705
			he standard genetic code	706
~			ne standard genetic code	,00

xviii Contents

APPENDIX 3 Statistical data for quantitative		APPENDIX 8 Hydrogen bonding interactions	728
structure-activity relationships (QSAR)	707	APPENDIX 9 Drug properties	730
APPENDIX 4 The action of nerves	711		
APPENDIX 5 Microorganisms	715	GLOSSARY	741
APPENDIX 6 Drugs and their trade names	717	GENERAL FURTHER READING	761
APPENDIX 7 Trade names and drugs	722	INDEX	763