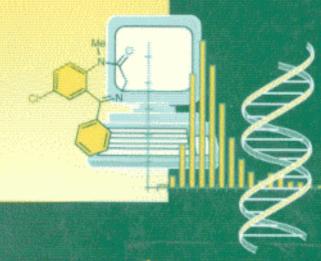
RS•C



medicinal chemistry

PRINCIPLES AND PRACTICE

Second Edition

edited by F.D.KING

Contents

Contributors				
Abbreviations				
General Re	ferences	xxvii		
Chapter 1	Drug-Receptor Interactions Rob Leurs			
	1 Introduction	1		
	2 Receptor Proteins	2		
	3 Mechanism of Drug Action: Agonism and			
	Antagonism	5		
	4 Receptor Subtypes	6		
•	5 Drug Selectivity	9		
	6 Quantification of Drug-Receptor Interactions	-10		
	The Receptor Binding of Ligands	11		
	From Receptor Binding to Effect	15		
•	The Occupation Theory of Clark	15		
	Partial Agonists and Intrinsic Activity	15		
	Partial Agonism and Drug Efficacy	16		
	Receptor Antagonism	18		
	7 From Antagonists to Inverse Agonists	21		
	8 Final Considerations	23		
	9 Selected Reading	23		
Chapter 2	An Introduction to Ion Channels	25		
* .	Brian Cox			
	1 Introduction	25		
	2 Structure, Function and Classification	~26		
	3 Representative Examples	29		
	Ligand-gated Channels	29		
	Voltage-gated Channels	34		
	Inward Rectifier and Miscellaneous Channels	38		
	4 Conclusion	40		
	5 References	40		

Chapter 3	Intracellular Targets	42				
	Eric Hunt, Neil Pearson, Timothy M. Willson and Andrew					
	Takle					
	1 Introduction	42				
	2 Antibacterial Inhibitors of Protein Synthesis	42				
	3 Bacterial Topoisomerase Inhibitors:					
	Fluoroquinolones	47				
	Mode of Action	47				
	Structure-Activity Relationships	47				
	Conclusions	52				
	4 Nuclear Receptors	52				
	Nature's Gene Switches	53				
	The Orphan Nuclear Receptors	55				
	Nuclear Receptors as Targets for Drug Discovery	57				
	5 Protein Kinases	57				
	Inhibition of Protein Kinases	59				
	Inhibitors of Epidermal Growth Factor Receptor					
	Kinase (EGFR)	60				
	Inhibitors of p38 MAP Kinase	61				
	Conclusion	62				
	6 References	62				
Chapter 4	Enzyme Inhibitors	64				
- -	David A. Roberts and Walter H.J. Ward	•				
	1 Introduction	64				
	2 Enzyme Inhibitor Categories	`67				
	Kinetics of Substrate Utilisation	67				
	IC ₅₀ Values Reflect Affinity and Assay Conditions	70				
	Mechanisms of Reversible Inhibition, Affinity and					
	Selectivity	72				
	Tight Binding Inhibitors	77				
	Slow Binding and Irreversible Inhibitors	77				
	3 Opportunities in Drug Design	79				
•	Exploitation of Enzyme Kinetics in Drug Discovery	79				
	Isothermal Titration Calorimetry	80				
	Structure-based Design	81				
	4 Classes of Enzymes and Examples of Enzyme	_				
	Inhibitors	82				
	Synthetases: Inhibition of Thymidylate Synthase	82				

		Reductases: Inhibition of Hydroxymethylglutaryl-	
		CoA Reductase (HMG-CoA Reductase)	83
		Kinases: Anilinoquinazolines as Inhibitors of	
		Protein Kinases	84
•		Proteases: Inhibition of Angiotensin Converting	
		Enzyme and Renin	85
	5	Concluding Remarks	89
		Acknowledgements	89
	6	References	90
		Additional Reading	90
Chapter 5		ological Evaluation of Novel Compounds	91
	Ga	ary W. Price, Graham J. Riley and Derek N. Middlen	iiss
	1	Introduction	91
	2	Primary Screens	93
		Broad Spectrum Evaluation of Compounds	99
		SB-236057	100
	3	Secondary Assays	101
		In Vitro Evaluation of Compounds	101
	•	Binding Assays in Native Tissue versus	
		Recombinant Systems	101
		Evaluation of Functional Activity of Compounds	102
		Agonists/Antagonists/Inverse Agonists	102
		Assays for Evaluating Functional Activity	103
		GTPγS Binding	104
		Reporter Gene Assays	107
		Measuring Function in Native Tissues	108
		[³ H]5HT Release from Brain Slices	109
	4	` '	111
	5	Pharmacodynamic Assays	111
		Requirements of a P.D. assay	111
		Examples of P.D. assays	112
		SB-236057	112
	6	Animal Models - Pre-clinical Proof of Concept	113
		Proof of Mechanism Models	114
		Disease Models	115
	7	Acknowledgements	116
	8	References	116

Chapter 6	Pharmacokinetics		
	Phillip Jeffrey	118	
	1 Introduction	118	
	2 The Process and Terminology of Drug Delive	ry 119	
	3 The Blood (or Plasma) Concentration—	•	
	Time Curve	120	
	4 Bioavailability	ļ	
	5 Clearance	5	
	6 Volume of Distribution)	
	7 Half-life	}	
	8 'Advanced' Pharmacokientic	j	
	9 Conclusions	137	
	10 References	137	
	11 Bibliography	137	
Chapter 7	Drug Metabolism	138	
	Stephen E. Clarke	100	
	1 Introduction	138	
	2 Distribution of Drug Metabolism Enzymes	138	
	3 The Drug Metabolising Enzymes	139	
	Phase I Metabolising Enzymes	141	
	Cytochrome P450	141	
	CYP3A4	142	
	CYP2D6	145	
	CYP2C9	145	
	CYP1A2	147	
	CYP2C19	147	
	CYP2C8	148	
	Other Oxidative Enzymes	148	
	Flavin Monooxygenase	148	
·	Monoamine Oxidase	149	
	Aldehyde Oxidase	149	
-	Xanthine Oxidase	150	
	Phase II Conjugation	150	
	Glucuronidation	150	
	Sulfation	151	
•	Acetylation	151	
	Glutathione	152	
	4 Conclusions	153	
	5 References and Bibliography	153	

Chapter 8	Toxicology in the Drug Discovery Process	155		
	Susan M. Evans, Elisabeth George and C. Westmorelan	ıd		
	1 Introduction	155		
•	2 Overview of Toxicity Assessment in Drug			
	Discovery	157		
	Disease Selection, Target Identification and Lead			
	Series Identification	158		
	Lead Compound Optimisation/Candidate			
	Compound Selection	159		
	Pre-clinical Safety Assessment and Clinical			
	Development	159		
	3 In Silico Systems for Assessing Toxicity	159		
	4 Introduction to In Vitro Systems	161		
	High Throughput Toxicity Screening	166		
	Cytotoxicity Screens Predictive of In Vivo			
	Toxicity	166		
	Cytotoxicity Screens Used to Assess In Vitro			
	Therapeutic Indices	168		
,	Cytotoxicity Screens Used to Validate Potential			
	Drug Candidates in Cellular Pharmacology			
	Screens	168		
	In vitro Screens for Specific Toxicities	169		
	Genetic Toxicology	169		
	Target Organ Toxicity	170		
	Hepatotoxicity	171		
	Nephrotoxicity	172		
	Haematotoxicity	172		
	5 In Vivo Toxicology in Candidate Selection	173		
	6 The Use of New Technologies in Safety			
	Assessment	176		
	Toxicogenomics	176		
	Proteomics	177		
	Nuclear Magnetic Resonance	178		
	7 Summary	1,79		
	8 References	179		
Chapter 9	Chemical Development			
	Paul Smith			
	1 Introduction	182		
	2 Illustrative Examples	190		

Chapter 10

	The Importance of Quality	19
	3,3-Dimethylindoline. An Example of Route	
_	Discovery and Development	19
3	Future Trends	19
4	Acknowledgement	19
5	References	19
	Further General Reading	19
	nysicochemical Properties an van de Waterbeemd	19
1	Introduction	
2		19
2	Dissolution and Solubility	19
	Measurement of Solubility	19
	Calculation of Solubility	19
3	Lipophilicity	19
_	Definitions and Lipophilicity Scales	20 20
	The Information Content in logP	20
	The Major Contributions	20:
	Diff $(\log P^{N-I})$	20:
	$\Delta \log P$	202
	Measurement of logD/logP	202
	From Shake-flask to High Throughput	202
	Difficulties with Alternative Solvent Systems	202
	Estimation of logP and logD	203
4	Hydrogen Bonding	`203
5	Molecular Size	204
6	Ionisation Constants	205
	Ionisation/Protonation State	205
_	Estimation of pK_a	206
7	Electronic Properties	207
8	Estimation of Other Molecular Properties	208
	Computational Properties	208
Δ.	Ligand-Receptor Interactions	208
9	Relationships to Drug Disposition	210
	Estimation of Gastrointestinal Absorption	210
	Estimation of Brain Penetration	211
10	Estimation of Pharmacokinetic Properties References	212
IU	INCICIONOES	212

Contents

Chapter 11	Quantitative Structure—Activity Relationships David J. Livingstone				
	1 Introduction	215			
,	2 Background to QSAR	217			
	3 Compound Selection	220			
	4 Describing Chemical Structure	223			
	5 Building QSAR Models	225			
	Multiple Linear Regression	226			
	Principle Component Methods	228			
	Data Display	230			
	Classified Data	232			
	3D QSAR	236			
	6 Artificial Intelligence	238			
	7 Summary	240			
	8 References	241			
Chapter 12	Computational Chemistry and Target Structure Colin Edge				
	1 Introduction – The Basic Toolkit	243			
	Graphics Programs	243			
•	Protein Modelling Programs	245			
	Programs That Combine Receptor and Ligand	246			
	Abstract Site Models	246			
	2 Structural Information for Computational	240			
•	Chemistry	246			
	X-ray Crystallography	246			
	Nuclear Magnetic Resonance	247			
	Structural Databases	247			
	3 The Use of Structure in Drug Design	248			
	Docking and Virtual Screening	248			
` .	Prediction of Binding Energies	249			
	De Novo Design	250			
	4 Related (Homologous) Structures	250			
	Protein Sequence Alignment	251			
	Homology Modelling	251			
	Membrane Proteins – Difficult Cases	252			
	5 The Absence of Target Structural Information	253			
	Quantitative Structure—Activity Relationships	253			
	Molecular Descriptors	254			

xvi Contents

	6	When the Target Structure Is Almost Irrelevant	254 254
		Drug Versus Leads	254
		Drug-like Qualities	255
	_	Blood-Brain Barrier	250
		Conclusion	257
	8	References	257
Chapter 13		ent Medicine	260
	Bill	! Tyrrell	
	1	Introduction	260
	2	What Are Patents?	262
	3	What Is Patentable?	26
		Novelty	265
		Inventive Step	266
	•	Sufficiency	267
		Utility or 'Industrial Application'	268
	4	'Patentese'	269
	5	Applying for Patents	27
	6	Prosecution and Litigation	276
	7	Trips and US Practice	278
	8	The Biotech Revolution	280
	9	Advance Module	283
	10	Sites for Sore Eyes	285
	A1	Conclusion	286
	12	References and Notes	287
Chapter 14		Introduction to Molecular Biology	291
	Kai	ph Rapley and Robert J. Slater	
	1	Introduction	291
	2	Nucleic Acids	291
	3	Proteins	293
	4	The Flow of Genetic Information	294
	5	DNA Replication	294
	6	Transcription	296
	7	RNA Processing	297
	8	Protein Synthesis	297
		Activation of Amino Acids	298
	_	Translation	299
	9	The Genetic Code	300
	10	Post Translational Modification	302

Contents	X	vii

	11	The Control of Transcription and Translation	302
	12	Genomics	302
	13	Nucleic Acid Analysis and Recombinant DNA	
1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -		Technology	304
1		Nucleic Acid Extraction Techniques	304
		Electrophoresis of Nucleic Acids	305
		Restriction Mapping of DNA Fragments	306
		Nucleic Acid Blotting and Hybridisation	307
		Production of Gene Probes	308
		DNA Gene Probe Labelling	309
		The Polymerase Chain Reaction	309
		Elements Involved in the PCR	310
		Primer Design in the PCR	311
		PCR Amplification Templates	312
		Applications of the PCR	313
		Recombinant DNA Technology and Gene	
		Libraries	315
		Digesting Genomic DNA Molecules	315
		Ligating DNA Molecules	315
•		Considerations in Gene Library Preparations	316
		Screening Gene Libraries	317
		Screening Expression cDNA Libraries	317
		Nucleotide Sequencing of DNA	319
		PCR Cycle Sequencing	321
		Automated Fluorescent DNA Sequencing	321
,		Maxam and Gilbert Sequencing	322
•	14	Bioinformatics and the Internet	322
	15	Human Genome Mapping Project	324
	16	References	`325
-			
Chapter 15	Str	ategy and Tactics in Drug Discovery	327
		nk D. King	327
			i 🙀
	1	Introduction	327
* .	2	Target Identification and Validation	328
	3	Lead Identification	330
•	4	Lead Optimisation	332
	5	Development Candidate	334
	6	Back-up/Follow-up	335
	7	Optimising the Chances for Success	335

.

xviii Contents

	8	Decision Making in Medicinal Chemistry	33
		Pharmacophore	33
		Bioisosteres	34
		Pharmacophoric Bioisosterism	34
		Template Bioisosterism	34
		Conformational Restriction	342
		Improved Affinity	344
		Improved Selectivity	34:
		Improved Chemical/Metabolic Stability	340
		Pro-drugs	34'
		Soft Drugs	356
		Data Interpretation	35
		Chemistry	35:
	9	Patents	35
	10	Conclusion	358
	11	References	358
Chapter 16	Cor	mbinatorial Chemistry: Tools for the Medicinal	
	Che	emist	359
,	Moi	rag A.M. Easson and David C. Rees	
	1	Introduction	359
	2	Concepts in Combinatorial Chemistry	360
		Compound Libraries and Arrays	360
/		Mix and Split Synthesis	361
	3	Impact of CC on the Drug Discovery Process	363
	4	Solid-phase Synthesis of 'Drug-like' Molecules	364
		Linkers and the Solid Support	364
		On-bead Monitoring	366
		Encoded Libraries	366
		Scope of Reactions and Structures on Solid Phase	367
		Singles Versus Mixtures	368
	5	Solution-phase Library Synthesis	368
		Strategies for Solution-phase Synthesis	368
		Parallel Solution-phase Libraries	369
		Support-bound Reagents and Scavengers	370
· .		Multi-component Condensations	371
•	6	Solid Phase Versus Solution Phase	372
	7	Laboratory Automation and Equipment	373
		Revolution at the Bench	373
		Synthesis	374
		Purification	376

Con	tents

Contents			xix
		Analysis	376
		Biological Activity from Compound Libraries	377
		Lead Generation Compound Libraries	377
		Lead Optimisation Compound Libraries	378
		Examples of Library Structures Demonstrating	
		Biological Activity	379
	9	Conclusions	379
	10	References	381
Chapter 17	The	Identification of Selective 5-HT _{2C} Receptor	
	Anta	agonists: A New Approach to the Treatment of	
	Depi	ression and Anxiety	382
	Steve	en M. Bromidge	
	1	Introduction to Depression	382
	2	Rationale for 5-HT _{2C} Antagonists in Depression	383
	3	Initial Lead: Identification of SB-200646	383
	4	Conformational Restriction: Identification of SB-206553	384
	5	Molecular and Receptor Modelling Studies	385
		Bioisosteric Replacement of the N-Methylindole	387
		Identification of Biarylcarbamoylindolines	391
		Bispyridyl Ethers: Identification of SB-243213	393
		Synthesis of SB-243213	394
		Summary	395
		References	395
	11	References	393
Chapter 18	The Identification of the HIV Protease Inhibitor		
	Saquinavir Frank D. King		397
	rran	k D. King	
		ntroduction	397
٠.		Primary Assay	399
		nhibitor Design	399
		dentification of the Minimum Inhibitor Sequence	399
		Optimisation of the N-terminus	400
-		Optimisation of the Proline	401
		X-ray Structures	404
		Synthesis of Saquinavir	405
		Clinical Data	405
		Conclusion	406
	7 F	References	406

XX	Contents
XX	Content

Chapter 19	Discovery of Vioxx (Rofecoxib) Frank D. King	
	11000 2.1106	
	1 Introduction	407
4.5	2 Lead Molecules	409
	3 Identification of Rofecoxib (MK-966)	410
	Assays	410
	Medicinal Chemistry	411
	4 In Vivo Activity of Rofecoxib	412
	5 Clinical Results	413
	6 Conclusion	414
	7 References	414
Chapter 20	NK1 Receptor Antagonists	415
	Chris Swain	
	1 Introduction	415
	2 Medicinal Chemistry Programme	416
	Reducing Calcium Channel Activity	417
•	Improving the Duration of Action	419
	Non-CNS Penetrant Compounds	421
	3 Profile of MK-869 Clinical Candidate	423
	4 Clinical Results	424
	Emesis	424
	Pain	425
	Psychiatric Indications	426
	Acknowledgements	427
	5 References	427
Appendices		
	1 Ranking of Key Ethical Drug Products in 2000 (US\$ Sales Value)	428
	2 Summary of Receptor Properties	430
	3 Plot of Molar Concentration vs. g ml ⁻¹ for	450
	Different Molecular Weights	440
	4 Table of Molar Concentration vs. g ml ⁻¹ for	
, •	Different Molecular Weights	441
	5 Conversion Table for $IC_{50}(K_i)$ to $pIC_{50}(pK_i)$	441
Subject Inde	x	442