

Contents

Preface *XIII*

List of Contributors *XV*

Part I General Aspects 1

1 Pioneer and Analogue Drugs 3

János Fischer, C. Robin Ganellin, and David P. Rotella

1.1 Monotarget Drugs 5

1.1.1 H₂ Receptor Histamine Antagonists 5

1.1.2 ACE Inhibitors 6

1.1.3 DPP IV Inhibitors 7

1.1.4 Univalent Direct Thrombin Inhibitors 8

1.2 Dual-Acting Drugs 10

1.2.1 Monotarget Drugs from Dual-Acting Drugs 10

1.2.1.1 Optimization of Beta-Adrenergic Receptor Blockers 10

1.2.2 Dual-Acting Drugs from Monotarget Drugs 11

1.2.2.1 Dual-Acting Opioid Drugs 11

1.3 Multitarget Drugs 12

1.3.1 Multitarget Drug Analogue to Eliminate a Side Effect 12

1.3.1.1 Clozapine and Olanzapine 12

1.3.2 Selective Drug Analogue from a Pioneer Multitarget Drug 13

1.3.2.1 Selective Serotonin Reuptake Inhibitors 13

1.4 Summary 16

Acknowledgments 16

References 16

2 Competition in the Pharmaceutical Drug Development 21

Christian Tyrchan and Fabrizio Giordanetto

2.1 Introduction 21

2.2 Analogue-Based Drugs: Just Copies? 22

2.3	How Often Does Analogue-Based Activity Occur? Insights from the GPCR Patent Space	25
	References	32
3	Metabolic Stability and Analogue-Based Drug Discovery	37
	<i>Amit S. Kalgutkar and Antonia F. Stepan</i>	
	List of Abbreviations	37
3.1	Introduction	37
3.2	Metabolism-Guided Drug Design	39
3.3	Indirect Modulation of Metabolism by Fluorine Substitution	42
3.4	Modulation of Low Clearance/Long Half-Life via Metabolism-Guided Design	45
3.5	Tactics to Resolve Metabolism Liabilities Due to Non-CYP Enzymes	46
3.5.1	Aldehyde Oxidase	46
3.5.2	Monoamine Oxidases	48
3.5.3	Phase II Conjugating Enzymes (UGT and Sulfotransferases)	49
3.6	Eliminating RM Liabilities in Drug Design	51
3.7	Eliminating Metabolism-Dependent Mutagenicity	51
3.8	Eliminating Mechanism-Based Inactivation of CYP Enzymes	54
3.9	Identification (and Elimination) of Electrophilic Lead Chemical Matter	60
3.10	Mitigating Risks of Idiosyncratic Toxicity via Elimination of RM Formation	61
3.11	Case Studies on Elimination of RM Liability in Drug Discovery	62
3.12	Concluding Remarks	67
	References	68
4	Use of Macrocycles in Drug Design Exemplified with Ulimorelin, a Potential Ghrelin Agonist for Gastrointestinal Motility Disorders	77
	<i>Mark L. Peterson, Hamid Hoveyda, Graeme Fraser, Éric Marsault, and René Gagnon</i>	
4.1	Introduction	77
4.1.1	Ghrelin as a Novel Pharmacological Target for GI Motility Disorders	77
4.1.2	Macrocycles in Drug Discovery	79
4.1.3	Tranzyme Technology	80
4.2	High-Throughput Screening Results and Hit Selection	82
4.3	Macrocycle Structure–Activity Relationships	83
4.3.1	Preliminary SAR	83
4.3.2	Ring Size and Tether	83
4.3.3	Amino Acid Components	87
4.3.4	Further Tether Optimization	89
4.4	PK–ADME Considerations	92
4.5	Structural Studies	95
4.6	Preclinical Evaluation	96

4.6.1	Additional Compound Profiling	97
4.6.2	Additional Pharmacokinetic Data	98
4.6.3	Animal Models for Preclinical Efficacy	100
4.7	Clinical Results and Current Status	100
4.8	Summary	103
	References	104
Part II	Drug Classes	111
5	The Discovery of Anticancer Drugs Targeting Epigenetic Enzymes	113
	<i>A. Ganesan</i>	
	List of Abbreviations	113
5.1	Epigenetics	114
5.2	DNA Methyltransferases	116
5.3	5-Azacytidine (Azacitidine, Vidaza) and 5-Aza-2'-deoxycytidine (Decitabine, Dacogen)	118
5.4	Other Nucleoside DNMT Inhibitors	122
5.5	Preclinical DNMT Inhibitors	123
5.6	Zinc-Dependent Histone Deacetylases	124
5.7	Suberoylanilide Hydroxamic Acid (SAHA, Vorinostat, Zolinza)	125
5.8	FK228 (Depsipeptide, Romidepsin, Istodax)	127
5.9	Carboxylic Acid and Benzamide HDAC Inhibitors	131
5.10	Prospects for HDAC Inhibitors	132
5.11	Epigenetic Drugs – A Slow Start but a Bright Future	133
	Acknowledgments	133
	References	134
6	Thienopyridyl and Direct-Acting P2Y₁₂ Receptor Antagonist Antiplatelet Drugs	141
	<i>Joseph A. Jakubowski and Atsuhiko Sugidachi</i>	
	List of Abbreviations	141
6.1	Introduction	142
6.1.1	Platelet Involvement in Atherothrombosis	142
6.2	Thienopyridines	143
6.2.1	Ticlopidine: 5-[(2-Chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2- <i>c</i>]pyridine	144
6.2.2	Clopidogrel: (+)-(S)- α -(2-Chlorophenyl)-6,7-dihydrothieno[3,2- <i>c</i>]pyridine-5(4 <i>H</i>) acetate	145
6.2.3	Prasugrel: 5-[(1 <i>RS</i>)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2- <i>c</i>]pyridin-2-yl acetate	147
6.3	Direct-Acting P2Y ₁₂ Antagonists	152
6.3.1	Nucleoside-Containing Antagonists	152
6.3.1.1	Cangrelor: [Dichloro-[[[(2 <i>R</i> ,3 <i>S</i> ,4 <i>R</i> ,5 <i>R</i>)-3,4-dihydroxy-5-[6-(2-methylsulfanylethylamino)-2-(3,3,3-trifluoropropylsulfanyl)purin-9-yl]oxolan-2-yl]methoxy-hydroxyphosphoryl]oxy-hydroxyphosphoryl]methyl]phosphonic acid	153

6.3.1.2	Ticagrelor: (1 <i>S</i> ,2 <i>S</i> ,3 <i>R</i> ,5 <i>S</i>)-3-[7-[(1 <i>R</i> ,2 <i>S</i>)-2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3 <i>H</i> -[1,2,3]triazolo[4,5- <i>d</i>]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol	154
6.3.2	Non-Nucleoside P2Y ₁₂ Antagonists	157
6.3.2.1	Elinogrel: <i>N</i> -[(5-Chlorothiophen-2-yl)sulfonyl]- <i>N'</i> -{4-[6-fluoro-7-(methylamino)-2,4-dioxo-1,4-dihydroquinazolin-3(2 <i>H</i>)-yl]phenyl}urea	157
6.4	Summary	158
	References	158
7	Selective Estrogen Receptor Modulators	165
	<i>Amarjit Luniwal, Rachael Jetson, and Paul Erhardt</i>	
	List of Abbreviations	165
7.1	Introduction	166
7.1.1	Working Definition	166
7.1.2	Early ABDD Leading to a Pioneer SERM	167
7.1.3	Discovery and Development of Clomiphene	169
7.1.4	SERM-Directed ABDD: General Considerations	170
7.2	Tamoxifen	171
7.2.1	Early Development	171
7.2.2	Clinical Indications and Molecular Action	172
7.2.3	Pharmacokinetics and Major Metabolic Pathways	174
7.2.4	Clinical Toxicity and New Tamoxifen Analogues	175
7.3	Raloxifene	175
7.3.1	Need for New Antiestrogens	176
7.3.2	Design and Initial Biological Data on Raloxifene	176
7.3.3	RUTH Study	177
7.3.4	STAR Study	177
7.3.5	Binding to the Estrogen Receptor	178
7.3.6	ADME	179
7.3.7	Further Research	179
7.4	Summary	179
	References	180
8	Discovery of Nonpeptide Vasopressin V₂ Receptor Antagonists	187
	<i>Kazumi Kondo and Hidenori Ogawa</i>	
	List of Abbreviations	187
8.1	Introduction	187
8.2	Peptide AVP Agonists and Antagonists	188
8.3	Lead Generation Strategies	189
8.4	Lead Generation Strategy-2, V ₂ Receptor Affinity	192
8.5	Lead Optimization	197
8.6	Reported Nonpeptide Vasopressin V ₂ Receptor Antagonist Compounds	199
8.6.1	Sanofi	199

8.6.2	Astellas (Yamanouchi)	199
8.6.3	Wyeth	201
8.6.4	Johnson & Johnson	201
8.6.5	Wakamoto Pharmaceutical Co. Ltd	202
8.6.6	Japan Tobacco Inc.	202
8.7	Conclusions	203
	References	203
9	The Development of Cysteinyl Leukotriene Receptor Antagonists	211
	<i>Peter R. Bernstein</i>	
	List of Abbreviations	211
9.1	Introduction	212
9.2	Scope of the Drug Discovery Effort on Leukotriene Modulators	214
9.3	Synthetic Leukotriene Production and Benefits Derived from this Effort	215
9.4	Bioassays and General Drug Discovery Testing Cascade	216
9.5	Development of Antagonists – General Approaches	218
9.6	Discovery of Zafirlukast	218
9.7	Discovery of Montelukast	224
9.8	Discovery of Pranlukast	227
9.9	Comparative Analysis and Crossover Impact	229
9.10	Postmarketing Issues	231
9.11	Conclusions	232
	Acknowledgment	232
	Disclaimer	232
	References	233
Part III	Case Studies	241
10	The Discovery of Dabigatran Etxilate	243
	<i>Norbert Hanel, Andreas Clemens, Herbert Nar, Henning Priepke, Joanne van Ryn, and Wolfgang Wien</i>	
	List of Abbreviations	243
10.1	Introduction	243
10.2	Dabigatran Design Story	246
10.3	Preclinical Pharmacology Molecular Mechanism of Action of Dabigatran	254
10.3.1	<i>In Vitro</i> Antithrombotic Effects of Dabigatran	255
10.3.2	<i>Ex Vivo</i> Antithrombotic Effects of Dabigatran/Dabigatran Etxilate	256
10.3.3	Venous and Arterial Antithrombotic Effects of Dabigatran/Dabigatran Etxilate	256
10.3.4	Mechanical Heart Valves	257
10.3.5	Cancer	257
10.3.6	Fibrosis	257
10.3.7	Atherosclerosis	258

10.4	Clinical Studies and Indications	258
10.4.1	Prevention of Deep Venous Thrombosis	259
10.4.2	Therapy of Venous Thromboembolism	259
10.4.3	Stroke Prevention in Patients with Atrial Fibrillation	260
10.4.4	Prevention of Recurrent Myocardial Infarction in Patients with Acute Coronary Syndrome	260
10.5	Summary	260
	References	261
11	The Discovery of Citalopram and Its Refinement to Escitalopram	269
	<i>Klaus P. Bøgesø and Connie Sánchez</i>	
	List of Abbreviations	269
11.1	Introduction	270
11.2	Discovery of Talopram	271
11.3	Discovery of Citalopram	272
11.4	Synthesis and Production of Citalopram	275
11.5	The Pharmacological Profile of Citalopram	276
11.6	Clinical Efficacy of Citalopram	277
11.7	Synthesis and Production of Escitalopram	278
11.8	The Pharmacological Profile of the Citalopram Enantiomers	279
11.9	R-Citalopram's Surprising Inhibition of Escitalopram	279
11.10	Binding Site(s) for Escitalopram on the Serotonin Transporter	283
11.11	Future Perspectives on the Molecular Basis for Escitalopram's Interaction with the SERT	286
11.12	Clinical Efficacy of Escitalopram	287
11.13	Conclusions	288
	References	288
12	Tapentadol – From Morphine and Tramadol to the Discovery of Tapentadol	295
	<i>Helmut Buschmann</i>	
	List of Abbreviations	295
12.1	Introduction	296
12.1.1	Pain and Current Pain Treatment Options	297
12.1.2	Pain Research Today	300
12.1.3	The Complex Mode of Action of Tramadol	301
12.2	The Discovery of Tapentadol	302
12.2.1	From the Tramadol Structure to Tapentadol	303
12.2.2	Synthetic Pathways to Tapentadol	306
12.3	The Preclinical and Clinical Profile of Tapentadol	310
12.3.1	Preclinical Pharmacology of Tapentadol	311
12.3.2	Clinical Trials	312
12.3.3	Pharmacokinetics and Drug–Drug Interactions of Tapentadol	314
12.4	Summary	315
	References	315

13	Novel Taxanes: Cabazitaxel Case Study	319
	<i>Hervé Bouchard, Dorothée Semiond, Marie-Laure Risse, and Patricia Vrignaud</i>	
	List of Abbreviations	319
13.1	Introduction	320
13.1.1	Isolation and Chemical Synthesis of Taxanes	321
13.1.2	Drug Resistance and Novel Taxanes	322
13.2	Cabazitaxel Structure–Activity Relationships and Chemical Synthesis	323
13.2.1	Chemical and Physical Properties	323
13.2.2	Structure–Activity Relationships of Cabazitaxel	324
13.2.3	Chemical Synthesis of Cabazitaxel	325
13.3	Cabazitaxel Preclinical and Clinical Development	328
13.3.1	Preclinical Development	328
13.3.2	Clinical Studies	330
13.3.2.1	Phase I and II Studies	332
13.3.2.2	Clinical Pharmacokinetics	333
13.3.2.3	Phase III Trial	334
13.3.3	Other Ongoing Trials	335
13.4	Summary	336
	Acknowledgments	337
	References	337
14	Discovery of Boceprevir and Narlaprevir: A Case Study for Role of Structure-Based Drug Design	343
	<i>Srikanth Venkatraman, Andrew Prongay, and George F. Njoroge</i>	
	List of Abbreviations	343
	References	359
15	A New-Generation Uric Acid Production Inhibitor: Febuxostat	365
	<i>Ken Okamoto, Shiro Kondo, and Takeshi Nishino</i>	
	List of Abbreviations	365
15.1	Introduction	365
15.2	Xanthine Oxidoreductase – Target Protein for Gout Treatment	367
15.3	Mechanism of XOR Inhibition by Allopurinol	368
15.4	Development of Nonpurine Analogue Inhibitor of XOR: Febuxostat	369
15.5	Mechanism of XOR Inhibition by Febuxostat	370
15.6	Excretion of XOR Inhibitors	372
15.7	Results of Clinical Trials of Febuxostat in Patients with Hyperuricemia and Gout	372
15.8	Summary	373
15.9	Added in proof	373
	References	373
	Index	377