

Contents

Preface *XIII*

List of Contributors *XVII*

Part I General Aspects *1*

- 1 Serendipitous Target-Based Drug Discoveries** *3*
János Fischer and David P. Rotella
 - 1.1 Introduction *3*
 - 1.2 Recent Examples of Target-Based Drug Discovery *4*
 - 1.3 Serendipitous Target-Based Drug Discoveries *7*
 - 1.4 Drospirenone (Contraceptive with Anti-aldosterone Activity) *7*
 - 1.4.1 Summary of Drospirenone Discovery *8*
 - 1.5 Escitalopram (Selective Serotonin Reuptake Inhibitor Antidepressant) *9*
 - 1.5.1 Summary of the Escitalopram Discovery *11*
 - 1.6 Ezetimibe (Inhibitor of Cholesterol Absorption) *11*
 - 1.6.1 Summary of Ezetimibe Discovery *13*
 - 1.7 Lamotrigine (Discovery of a Standalone Drug for the Treatment of Epilepsy) *13*
 - 1.7.1 Summary of Lamotrigine Discovery *15*
 - 1.8 Omeprazole (Proton Pump Inhibitor Acid-Suppressive Agent) *15*
 - 1.8.1 Summary of Omeprazole Discovery *16*
 - 1.9 Outlook *17*
Acknowledgments *17*
List of Abbreviations *17*
References *18*
- 2 Drug Discoveries and Molecular Mechanism of Action** *19*
David C. Swinney
 - 2.1 Introduction *19*
 - 2.2 Mechanistic Paradox *19*
 - 2.3 Molecular Mechanism of Action *20*

2.3.1	The Primary Driver of an Optimal MMOA is the Potential for Mechanism-Based Toxicity	22
2.3.2	Details of MMOA are not Captured by IC ₅₀ and K _i	22
2.3.3	Metrics, Biochemical Efficiency	24
2.4	How MMOAs were Discovered	25
2.4.1	MMOAs of Medicines Approved by the USFDA Between 1999 and 2008	27
2.5	Case Study: Artemisinin	30
2.6	Summary	31
	List of Abbreviations	32
	References	32

Part II Drug Class 35

3	Insulin Analogs – Improving the Therapy of Diabetes	37
	<i>John M. Beals</i>	
3.1	Introduction	37
3.2	Pharmacology and Insulin Analogs	38
3.3	Chemical Description	39
3.4	Rapid-Acting Insulin Analogs (Prandial or Bolus Insulin)	41
3.5	Long-Acting Insulin Analog Formulations (Basal Insulin)	48
3.6	Conclusions and Future Considerations	54
	List of Abbreviations	55
	References	55

Part III Case Histories 61

4	The Discovery of Stendra™ (Avanafil) for the Treatment of Erectile Dysfunction	63
	<i>Koichiro Yamada, Toshiaki Sakamoto, Kenji Omori, and Kohei Kikkawa</i>	
4.1	Introduction	63
4.2	Discovery of Avanafil	65
4.2.1	Differentiation Strategies to Develop a New Drug	65
4.2.2	Discovery of Isoquinoline Derivatives from Isoquinolinone Lead	65
4.2.3	Scaffold-Hopping Approaches from the Isoquinoline Leads	67
4.2.3.1	Monocyclic Type A Series: Tetrasubstituted Pyrimidine Derivatives	68
4.2.3.2	Monocyclic Type B Series: Trisubstituted Pyrimidine Derivatives	68
4.2.3.3	SAR of Substitution at the 2-Position of the Pyrimidine Ring (15)	70
4.2.3.4	SAR of Substitution at the 4-Position of the Pyrimidine Ring (16)	70
4.2.3.5	SAR of Substitution at the 5-Position of the Pyrimidine Ring (19, 20)	73
4.2.3.6	Core Structure Modifications of the Pyrimidine Nucleus of Avanafil	73

4.3	Pharmacological Features of Avanafil	75
4.3.1	PDE Inhibitory Profiles	75
4.3.2	<i>In Vivo</i> Pharmacology	76
4.3.2.1	Potential of Penile Tumescence in Dogs	76
4.3.2.2	Influence on Retinal Function in Dogs	79
4.3.2.3	Influence on Hemodynamics in Dogs	79
4.3.2.4	Influence on Nitroglycerin (NTG)-Induced Hypotension in Dogs	80
4.4	Clinical Studies of Avanafil	81
4.5	Conclusion	83
	List of Abbreviations	83
	References	83
5	Dapagliflozin, A Selective SGLT2 Inhibitor for Treatment of Diabetes	87
	<i>William N. Washburn</i>	
5.1	Introduction	87
5.2	Role of SGLT2 Transporters in Renal Function	88
5.3	O-Glucoside SGLT2 Inhibitors	89
5.3.1	Hydroxybenzamide O-Glucosides	90
5.3.2	Benzylpyrazolone O-Glucosides	94
5.3.3	<i>o</i> -Benzylphenol O-Glucosides	95
5.4	<i>m</i> -Diarylmethane C-Glucosides	97
5.4.1	Synthetic Route	98
5.4.2	Early SAR of C-Glucoside Based SGLT2 Inhibitors	99
5.4.3	Identification of Dapagliflozin	102
5.5	Profiling Studies with Dapagliflozin	105
5.6	Clinical Studies with Dapagliflozin	108
5.7	Summary	108
	List of Abbreviations	109
	References	110
6	Elvitegravir, A New HIV-1 Integrase Inhibitor for Antiretroviral Therapy	113
	<i>Hisashi Shinkai</i>	
6.1	Introduction	113
6.2	Discovery of Elvitegravir	114
6.2.1	HIV-1 Integrase and Diketo Acid Inhibitors	114
6.2.2	Monoketo Acid Integrase Inhibitors and Elvitegravir	116
6.3	Conclusion	121
	List of Abbreviations	123
	References	123

7	Discovery of Linagliptin for the Treatment of Type 2 Diabetes Mellitus 129
	<i>Matthias Eckhardt, Thomas Klein, Herbert Nar, and Sandra Thiemann</i>
7.1	Introduction 129
7.2	Discovery of Linagliptin – High Throughput Screening Hit Optimization 130
7.3	Rationalization of DPP-4 Inhibition Potency by Crystal Structure Analysis and Studies of Binding Kinetics 139
7.4	Basic Physicochemical, Pharmacological, and Kinetic Characteristics 141
7.5	Preclinical Studies 143
7.5.1	Glucose Regulation by Linagliptin 143
7.5.2	Effects of Linagliptin on the Kidney 145
7.6	Clinical Studies 146
7.6.1	Clinical Pharmacokinetics 146
7.6.2	Clinical Pharmacodynamics 148
7.6.2.1	Inhibition of DPP-4 148
7.6.2.2	Effects on Glucagon-Like Peptide-1 and Hyperglycemia 148
7.6.3	Clinical Use in Special Patient Populations 148
7.6.3.1	Patients with Renal Impairment 148
7.6.3.2	Patients with Hepatic Impairment 150
7.6.4	Cardiovascular Safety 150
7.7	Conclusion 151
	List of Abbreviations 151
	References 152
8	The Discovery of Alimta (Pemetrexed) 157
	<i>Edward C. Taylor</i>
	List of Abbreviations 175
	References 176
9	Perampanel: A Novel, Noncompetitive AMPA Receptor Antagonist for the Treatment of Epilepsy 181
	<i>Shigeki Hibi</i>
9.1	Introduction 181
9.1.1	Competitive Receptor Antagonists 182
9.1.2	Noncompetitive Receptor Antagonists 182
9.2	Seeds Identification by High Throughput Screening (HTS) Assays 183
9.3	Structure and Activity Relationship (SAR) Study Starting from the Unique Structure of Seed Compounds 184
9.3.1	Introduction of Conjugated Aromaticity 184
9.3.2	Discovery of 1,3,5-Triaryl-1 <i>H</i> -pyridin-2-one Template 184
9.3.3	Optimization of 1,3,5-Triaryl-1 <i>H</i> -pyridin-2-one Derivatives 185

9.4	Pharmacological Properties of Perampanel; Selection for Clinical Development	187
9.4.1	The Pharmacological Evaluation of Perampanel	187
9.4.2	The Pharmacokinetic Evaluation of Perampanel	189
9.5	Clinical Development of Perampanel	189
9.5.1	Phase I	189
9.5.2	Phase II and Phase III	190
9.6	Conclusion	190
	List of Abbreviations	190
	References	191
10	Discovery and Development of Telaprevir (Incivek™) – A Protease Inhibitor to Treat Hepatitis C Infection	195
	<i>Bhisetti G. Rao, Mark A. Murcko, Mark J. Tebbe, and Ann D. Kwong</i>	
10.1	Introduction	195
10.1.1	Crystal Structure of NS3/4A Protease	196
10.1.2	Assays	196
10.2	Discussion	197
10.2.1	Substrate-Based Inhibitor Design	197
10.2.2	Structure-Based Inhibitor Optimization	200
10.2.3	Pre-Clinical Development	206
10.2.4	Clinical Development	206
10.3	Summary	207
	List of Abbreviations	208
	References	209
11	Antibody–Drug Conjugates: Design and Development of Trastuzumab Emtansine (T-DM1)	213
	<i>Sandhya Girish, Gail D. Lewis Phillips, Fredric S. Jacobson, Jagath R. Junutula, and Ellie Guardino</i>	
11.1	Introduction	213
11.2	Molecular Design of T-DM1	214
11.3	Strategies for Bioanalysis	216
11.4	Strategies for Chemistry and Manufacturing Control	218
11.5	Nonclinical Development	219
11.6	Clinical Pharmacology	220
11.7	Clinical Trials and Approval	222
11.8	Summary	224
	List of Abbreviations	225
	References	226
	Index	231