## CONTENTS

### PREFACE  xv

### CONTRIBUTORS  xvii

### CHAPTER 1  INTRODUCTION: DRUG DISCOVERY IN DIFFICULT TIMES  1

Malcolm MacCoss

### CHAPTER 2  DISCOVERY AND DEVELOPMENT OF THE DPP-4 INHIBITOR JANUVIA™ (SITA-GLIPTIN)  10

Emma R. Parmee, Ranabir SinhaRoy, Feng Xu, Jeffrey C. Givand, and Lawrence A. Rosen

2.1 Introduction  10

2.2 DPP-4 Inhibition as a Therapy for Type 2 Diabetes: Identification of Key Determinants for Efficacy and Safety  10

2.2.1 Incretin-Based Therapy for T2DM  10

2.2.2 Biological Rationale: DPP-4 is a Key Regulator of Incretin Activity  11

2.2.3 Injectable GLP-1 Mimetics for the Treatment of T2DM  12

2.2.4 DPP-4 Inhibition as Oral Incretin-Based Therapy for T2DM  12

2.2.5 Investigation of DPP-4 Biology: Identification of Candidate Substrates  13

2.2.6 Preclinical Toxicities of In-Licensed DPP-4 Inhibitors  15

2.2.7 Correlation of Preclinical Toxicity with Off-Target Inhibition of Pro-Specific Dipeptidase Activity  16

2.2.8 Identification of Pro-Specific Dipeptidases Differentially Inhibited by the Probiodrug Compounds  17

2.2.9 A Highly Selective DPP-4 Inhibitor is Safe and Well Tolerated in Preclinical Species  19

2.2.10 A Highly Selective DPP-4 Inhibitor Does Not Inhibit T-Cell Proliferation in vitro  19

2.2.11 DPP-4 Inhibitor Selectivity as a Key Parameter for Drug Development  20

2.3 Medicinal Chemistry Program  20

2.3.1 Lead Generation Approaches  20

2.3.2 Cyclohexyl Glycine \( \alpha \)-Amino Acid Series of DPP-4 Inhibitors  20

2.3.3 Improving Selectivity of the \( \alpha \)-Amino Acid Series  22

2.3.4 Identification and Optimization of the \( \beta \)-Amino Acid Series  22

2.4 Synthetic and Manufacturing Routes to Sitagliptin  27

2.4.1 Medicinal Chemistry Route to Sitagliptin and Early Modifications  27

2.4.2 An Asymmetric Hydrogenation Manufacturing Route to Sitagliptin  28

2.4.3 A “Greener” Manufacturing Route to Sitagliptin Employing Biocatalytic Transamination  31

2.5 Drug Product Development  33

2.5.1 Overview  33

2.5.2 Composition Development  33

2.5.3 Manufacturing Process Development  33

2.6 Clinical Studies  36
CONTENTS

2.6.1 Preclinical PD Studies and Early Clinical Development of Sitagliptin 36
2.6.2 Summary of Phase II/III Clinical Trials 38
2.7 Summary 39
References 39

CHAPTER 3  OLMESARTAN MEDOXOMIL: AN ANGIOTENSIN II RECEPTOR BLOCKER 45

Hiroaki Yanagisawa, Hiroyuki Koike, and Shin-ichiro Miura

3.1 Background 45
3.1.1 Introduction 45
3.1.2 Prototype of Orally Active ARBs 46
3.2 The Discovery of Olmesartan Medoxomil (Benicar) 47
3.2.1 Lead Generation 47
3.2.2 Lead Optimization 49
3.3 Characteristics of Olmesartan 53
3.4 Binding Sites of Omlersartan to the AT₁ Receptor and Its Inverse Agonoist Activity 56
3.4.1 Binding Sites of Olmesartan to the AT₁ Receptor 56
3.4.2 Inverse Agonist Activity of Olmesartan 56
3.4.3 Molecular Model of the Interaction between Olmesartan and the AT₁ Receptor 57
3.5 Practical Preparation of Olmesartan Medoxomil 58
3.6 Preclinical Studies 58
3.6.1 AT₁ Receptor Blocking Action 58
3.6.2 Inhibition of Ang II-Induced Vascular Contraction 59
3.6.3 Inhibition of the Pressor Response to Ang II 60
3.6.4 Blood Pressure Lowering Effects 60
3.6.5 Organ Protection 61
3.7 Clinical Studies 62
3.7.1 Antihypertensive Efficacy and Safety 62
3.7.2 Organ Protection 63
3.8 Conclusion 63
References 64

CHAPTER 4  DISCOVERY OF HETEROCYCLIC PHOSPHONIC ACIDS AS NOVEL AMP MIMICS THAT ARE POTENT AND SELECTIVE FRUCTOSE-1,6-BISPHOSPHATASE INHIBITORS AND ELICIT POTENT GLUCOSE-LOWERING EFFECTS IN DIABETIC ANIMALS AND HUMANS 67

Qun Dang and Mark D. Erion

4.1 Introduction 67
4.2 The Discovery of MB06322 69
4.2.1 Research Operation Plan 69
4.2.2 Discovery of Nonnucleotide AMP Mimics as FBPase Inhibitors 69
4.2.3 Discovery of Benzimidazole Phosphonic Acids as FBPase Inhibitors 74
4.2.4 Discovery of Thiazole Phosphonic Acids as Potent and Selective FBPase Inhibitors 77
4.2.5 The Discovery of MB06322 Through Prodrug Strategy 80
4.3 Pharmacokinetic Studies of MB06322 82
4.4 Synthetic Routes to MB06322 83
4.5 Clinical Studies of MB06322 83
4.5.1 Efficacy Study of Thiazole 12.6 in Rodent Models of T2DM 83
4.5.2 Phase I/II Clinical Studies 84
4.6 Summary 84
References 85
CONTENTS

7.7 In Vivo Profile of FQIT 146
  7.7.1 In Vivo Pharmacodynamic and PK/PD Correlation 146
  7.7.2 In Vivo Efficacy 146

7.8 Safety Assessment and Selectivity Profile of FQIT 148
  7.8.1 Effects on Blood Glucose and Insulin Levels 148
  7.8.2 Oral Glucose Tolerance Test 148
  7.8.3 Ames, Rodent, and Nonrodent Toxicology Studies 149
  7.8.4 Selectivity Profile of FQIT 149

7.9 Summary 150
Acknowledgments 151
References 151

CHAPTER 8 DISCOVERY AND DEVELOPMENT OF MONTELUKAST (SINGULAIR®) 154
Robert N. Young

8.1 Introduction 154
8.2 Drug Development Strategies 158
8.3 LTD3 Antagonist Program 159
  8.3.1 Lead Generation and Optimization 159
  8.3.2 In Vitro and In Vivo Assays 159
8.4 The Discovery of Montelukast (Singulair®) 160
  8.4.1 First-Generation Antagonists (Figure 8.3) 160
  8.4.2 Discovery of MK-571 163
  8.4.3 Discovery of MK-0679 (29) 168
  8.4.4 Discovery of Montelukast (L-706,631, MK-0476, Singulair®) 171
8.5 Synthesis of Montelukast 174
  8.5.1 Medicinal Chemistry Synthesis 174
  8.5.2 Process Chemistry Synthesis [104, 105] (Schemes 8.5 and 8.6) 176
8.6 ADME Studies with MK-0476 (Montelukast) 179
8.7 Safety Assessment of Montelukast 180
8.8 Clinical Development of Montelukast 180
  8.8.1 Human Pharmacokinetics, Safety, and Tolerability 180
  8.8.2 Human Pharmacology 181
  8.8.3 Phase 2 Studies in Asthma 182
  8.8.4 Phase 3 Studies in Asthma 182
  8.8.5 Effects of Montelukast on Inflammation 185
  8.8.6 Montelukast and Allergic Rhinitis 185
8.9 Summary 185
  8.9.1 Impact on Society 185
  8.9.2 Lessons Learned 186
8.10 Personal Impact 187
References 188

CHAPTER 9 DISCOVERY AND DEVELOPMENT OF MARAVIROC, A CCR5 ANTAGONIST FOR THE TREATMENT OF HIV INFECTION 196
Patrick Dorr, Blanda Stammen, and Elna van der Ryst

9.1 Background and Rationale 196
9.2 The Discovery of Maraviroc 199
  9.2.1 HTS and Biological Screening to Guide Medicinal Chemistry 199
  9.2.2 Hit Optimization 200
  9.2.3 Overcoming Binding to hERG 201
9.3 Preclinical Studies 201
  9.3.1 Metabolism and Pharmacokinetic Characteristics of Maraviroc 201
CONTENTS

9.3.2 Maraviroc Preclinical Pharmacology 202
9.3.3 Preclinical Investigations into HIV Resistance 202
9.3.4 Binding of Maraviroc to CCR5 204
9.4 The Synthesis of Maraviroc 205
9.5 Nonclinical Safety and Toxicity Studies 206
9.5.1 Safety Pharmacology 206
9.5.2 Immuno- and Mechanistic Toxicity 206
9.6 Clinical Development of Maraviroc 207
9.6.1 Phase 1 Studies 207
9.6.2 Phase 2a Studies 209
9.6.3 Phase 2b/3 Studies 210
9.6.4 Development of Resistance to CCR5 Antagonists In Vivo 213
9.7 Summary, Future Directions, and Challenges 214
Acknowledgments 217
References 217

CHAPTER 10 DISCOVERY OF ANTIMALARIAL DRUG ARTEMISININ AND BEYOND 227

Weiwei Mao, Yu Zhang, and Ao Zhang

10.1 Introduction: Natural Products in Drug Discovery 227
10.2 Natural Product Drug Discovery in China 227
10.3 Discovery of Artemisinin: Background, Structural Elucidation and Pharmacological Evaluation 228
10.3.1 Background and Biological Rationale 228
10.3.2 The Discovery of Artemisinin through Nontraditional Drug Discovery Process 229
10.3.3 Structural Determination of Artemisinin 231
10.3.4 Pharmacological Evaluation and Clinical Summary of Artemisinin 231
10.4 The Synthesis of Artemisinin 232
10.4.1 Synthesis of Artemisinin using Photooxidation of Cyclic or Acyclic Enol Ether as the Key Step 233
10.4.2 Synthesis of Artemisinin by Photooxidation of Dihydroartannuic Acid 236
10.4.3 Synthesis of Artemisinin by Ozonolysis of a Vinylsilane Intermediate 236
10.5 SAR Studies of Structural Derivatives of Artemisinin: The Discovery of Artemether 238
10.5.1 C-10-Derived Artemisinin Analogs 240
10.5.2 C-9 and C-9,10 Double Substituted Analogs 245
10.5.3 C-3 Substituted Analogs 246
10.5.4 C-6 or C-7 Substituted Derivatives 246
10.5.5 C-11-Substituted Analogs 247
10.6 Development of Artemether 248
10.6.1 Profile and Synthesis of Artemether 248
10.6.2 Clinical Studies Aspects of Artemether 249
10.7 Conclusion and Perspective 250
Acknowledgment 250
References 251

CHAPTER 11 DISCOVERY AND PROCESS DEVELOPMENT OF MK-4965, A POTENT NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR 257

Yong-Li Zhong, Thomas J. Tucker, and Jingjun Yin

11.1 Introduction 257
11.2 The Discovery of MK-4965 260
11.2.1 Background Information 260
11.2.2 SAR Studies Leading to the Discovery of MK-4965 262
11.3 Preclinical and Clinical Studies of MK-4965 (19) 266
CONTENTS

11.4 Summary of Back-Up SAR Studies of MK-4965 Series 266
11.5 Process Development of MK-4965 (19) 267
   11.5.1 Medicinal Chemistry Route 267
   11.5.2 Process Development 269
11.6 Conclusion 290
   11.6.1 Lessons Learned from the Medicinal Chemistry Effort of MK-4965 Discovery 290
   11.6.2 Summary and Lessons Learned from the Process Development of MK-4965 291
Acknowledgments 291
References 291

CHAPTER 12 DISCOVERY OF BOCEPREVIR AND NARLAPREVIR: THE FIRST AND SECOND GENERATION OF HCV NS3 PROTEASE INHIBITORS 296

Kevin X. Chen and F. George Njoroge

12.1 Introduction 296
12.2 HCV NS3 Protease Inhibitors 298
12.3 Research Operation Plan and Biological Assays 302
   12.3.1 Research Operation Plan 302
   12.3.2 Enzyme Assay 302
   12.3.3 Replicon Assay 302
   12.3.4 Measure of Selectivity 303
12.4 Discovery of Boceprevir 303
   12.4.1 Initial Lead Generation Through Structure-Based Drug Design 303
   12.4.2 SAR Studies Focusing on Truncation, Depeptization, and Macrocyclisation 304
   12.4.3 Individual Amino Acid Residue Modifications 307
   12.4.4 Correlations Between P1, P3, and P3 Capping: The Identification of Boceprevir 315
12.5 Profile of Boceprevir 317
   12.5.1 In Vitro Characterization of Boceprevir 317
   12.5.2 Pharmacokinetics of Boceprevir 317
   12.5.3 The Interaction of Boceprevir with NS3 Protease 318
12.6 Clinical Development and Approval of Boceprevir 319
12.7 Synthesis of Boceprevir 319
12.8 Discovery of Narlaprevir 322
   12.8.1 Criteria for the Back-up Program of Boceprevir 322
   12.8.2 SAR Studies 322
   12.8.3 Profile of Narlaprevir 326
   12.8.4 Clinical Development Aspects of Narlaprevir 327
   12.8.5 Synthesis of Narlaprevir 327
12.9 Summary 329
References 330

CHAPTER 13 THE DISCOVERY OF SAMSCA® (TOLVAPTAN): THE FIRST ORAL NONPEPTIDE VASOPRESSIN RECEPTOR ANTAGONIST 336

Kazumi Kondo and Yoshitaka Yamamura

13.1 Background Information about the Disease 336
13.2 Biological Rational 337
13.3 Lead Generation Strategies: The Discovery of Mozavaptan 338
13.4 Lead Optimization: From Mozavaptan to Tolvaptan 347
13.5 Pharmacological Profiles of Tolvaptan 350
   13.5.1 Antagonistic Affinities of Tolvaptan for AVP Receptors 350
   13.5.2 Aquaretic Effect Following a Single Dose in Conscious Rats 352
13.6 Drug Development 353
   13.6.1 Synthetic Route of Discovery and Commercial Synthesis [10a] 353
13.6.2 Nonclinical Toxicology 353
13.6.3 Clinical Studies 355
13.7 Summary Focusing on Lessons Learned 356
Acknowledgments 357
References 357

CHAPTER 14  SILODOSIN (URIEL®, RAPAFLO®, THRUPAS®, UROREC®, SILODIX™): A SELECTIVE $\alpha_{1A}$ ADRENOCEPTOR ANTAGONIST FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA 360

Masaki Yoshida, Imao Mikoshiba, Katsuyoshi Akiyama, and Junzo Kudoh

14.1 Background Information 360
14.1.1 Benign Prostatic Hyperplasia 360
14.1.2 $\alpha_1$-Adrenergic Receptors 361
14.2 The Discovery of Silodosin 362
14.2.1 Medicinal Chemistry 362
14.2.2 The Synthesis of Silodosin (Discovery Route) 363
14.2.3 Receptor Binding Studies 365
14.3 Pharmacology of Silodosin 369
14.3.1 Action Against Noradrenalin-Induced Contraction of Lower Urinary Tract Tissue 369
14.3.2 Actions Against Phenylephrine-Induced Increase in Intraurethral Pressure and Blood Pressure 371
14.3.3 Actions Against Intraurethral Pressure Increased by Stimulating Hypogastric Nerve and Blood Pressure in Dogs with Benign Prostatic Hyperplasia 372
14.3.4 Safety Pharmacology 373
14.4 Metabolism of Silodosin 373
14.5 Pharmacokinetics of Silodosin 376
14.5.1 Absorption 376
14.5.2 Organ Distribution 377
14.5.3 Excretion 378
14.6 Toxicology of Silodosin 379
14.7 Clinical Trials 382
14.7.1 Phase I Studies 382
14.7.2 Phase III Randomized, Placebo-Controlled, Double-Blind Study 383
14.7.3 Long-Term Administration Study 385
14.8 Summary: Key Lessons Learned 388
References 389

CHAPTER 15  RALOXIFENE: A SELECTIVE ESTROGEN RECEPTOR MODULATOR (SERM) 392

Jeffrey A. Dodge and Henry U. Bryant

15.1 Introduction: SERMs 392
15.2 The Benzothiophene Scaffold: A New Class of SERMs 394
15.3 Assays for Biological Evaluation of Tissue Selectivity 394
15.4 Benzothiophene Structure Activity 395
15.5 The Synthesis of Raloxifene 401
15.6 SERM Mechanism 402
15.7 Raloxifene Pharmacology 405
15.7.1 Skeletal System 405
15.7.2 Reproductive System—Uterus 407
15.7.3 Reproductive System—Mammary 408
15.7.4 General Safety Profile and Other Pharmacological Considerations 410
CONTENTS

15.8 Summary 411
References 411

APPENDIX I SMALL MOLECULE DRUG DISCOVERY AND DEVELOPMENT PARADIGM 417

APPENDIX II GLOSSARY 419

APPENDIX III ABBREVIATIONS 432

INDEX 443