Contents

Preface xi
Contributors xiii

I. Infectious Diseases 1

Chapter 1. Raltegravir (Isentress): The First-in-Class HIV-1 Integrase Inhibitor 3
Julianne A. Hunt
  1.1 Background 3
  1.2 Pharmacology 5
  1.3 Structure–Activity Relationship (SAR) 6
  1.4 Pharmacokinetics and Drug Metabolism 8
  1.5 Efficacy and Safety 9
  1.6 Syntheses 10
  1.7 References 13

Chapter 2. Maraviroc (Selzentry): The First-in-Class CCR5 Antagonist for the Treatment of HIV 17
David Price
  2.1 Background 17
  2.2 Structure–Activity Relationship (SAR) 19
  2.3 Pharmacokinetics and Safety 21
  2.4 Syntheses 22
  2.5 References 27

Chapter 3. Darunavir (Prezista): A HIV-1 Protease Inhibitor for Treatment of Multidrug Resistant HIV 29
Arun K. Ghosh and Cuthbert D. Martyr
  3.1 Background 29
  3.2 Pharmacology 32
  3.3 Structure–Activity Relationship (SAR) 32
  3.4 Pharmacokinetics and Drug Metabolism 33
  3.5 Efficacy and Safety 33
  3.6 Syntheses 34
  3.7 References 42
II. Cancer

Chapter 4. Decitabine (Dacogen): A DNA Methyltransferase Inhibitor for Cancer 47
Jennifer A. Van Camp

4.1 Background 47
4.2 Pharmacology 49
4.3 Structure–Activity Relationship (SAR) 49
4.4 Pharmacokinetics and Drug Metabolism 50
4.5 Efficacy and Safety 50
4.6 Syntheses 51
4.7 References 54

Chapter 5. Capecitabine (Xeloda): An Oral Chemotherapy Agent 57
R. Jason Herr

5.1 Background 57
5.2 Pharmacology 60
5.3 Structure–Activity Relationship (SAR) 62
5.4 Pharmacokinetics and Efficacy 63
5.5 Syntheses 64
5.6 References 70

Chapter 6. Sorafenib (Nexavar): A Multikinase Inhibitor for Advanced Renal Cell Carcinoma and Unresectable Hepatocellular Carcinoma 73
Shuanghua Hu and Yanzhong Huang

6.1 Background 73
6.2 Pharmacology 75
6.3 Structure–Activity Relationship (SAR) 77
6.4 Pharmacokinetics and Drug Metabolism 78
6.5 Efficacy and Safety 78
6.6 Syntheses 79
6.7 References 84

Chapter 7. Sunitinib (Sutent): An Angiogenesis Inhibitor 87
Martin Pettersson

7.1 Background 87
7.2 Discovery and Development 89
7.3 Syntheses 91
7.3.1 Discovery Route 91
7.3.2 Process Route 92
7.4 References 97
Chapter 8. Bortezomib (Velcade): A First-in-Class Proteasome Inhibitor 99

Benjamin S. Greener and David S. Millan
8.1 Background 99
8.2 Pharmacology 101
8.3 Structure–Activity Relationship (SAR) 102
8.4 Pharmacokinetics and Drug Metabolism 104
8.5 Efficacy and Safety 104
8.6 Syntheses 105
8.7 References 109

Chapter 9. Pazopanib (Votrient): A VEGFR Tyrosine Kinase Inhibitor for Cancer 111

Ji Zhang and Jie Jack Li
9.1 Background 111
9.2 Pharmacology 113
9.3 Structure–Activity Relationship (SAR) 114
9.4 Pharmacokinetics and Drug Metabolism 117
9.5 Efficacy and Safety 118
9.6 Syntheses 118
9.7 Other VEGFR Inhibitors in Development: Vandetanib and Cediranib 120
9.8 References 121

III. Cardiovascular and Metabolic Diseases 123

Chapter 10. Sitagliptin (Januvia): A Treatment for Type 2 Diabetes 125

Scott D. Edmondson, Feng Xu, and Joseph D. Armstrong III
10.1 Background 125
10.2 Pharmacology 126
10.3 Structure–Activity Relationship (SAR) 127
10.4 Pharmacokinetics and Drug Metabolism 128
10.5 Efficacy and Safety 129
10.6 Syntheses 130
10.7 References 138

Chapter 11. Aliskiren (Tekturna), The First-in-Class Renin Inhibitor for Hypertension 141

Victor J. Cee
11.1 Background 141
11.2 Pharmacology 144
11.3 Structure–Activity Relationship (SAR) 145
11.4 Pharmacokinetics and Drug Metabolism 146
11.5 Efficacy and Safety 147
11.6 Syntheses 148
11.7 References 156
Chapter 12. Vernakalant (Kynapid): An Investigational Drug for the Treatment of Atrial Fibrillation  
*David L. Gray*

12.1 Background  
12.2 Pharmacology  
12.3 Structure–Activity Relationship (SAR)  
12.4 Pharmacokinetics and Drug Metabolism  
12.5 Efficacy and Safety  
12.6 Syntheses  
12.7 References  

Chapter 13. Conivaptan (Vaprisol), Vasopressin V1a and V2 Antagonist for Hyponatremia  
*Brian A. Lanman*

13.1 Background  
13.2 Pharmacology  
13.3 Structure–Activity Relationship (SAR)  
13.4 Pharmacokinetics and Drug Metabolism  
13.5 Efficacy and Safety  
13.6 Syntheses  
13.7 References  

Chapter 14. Rivaroxaban (Xarelto): A Factor Xa Inhibitor for the Treatment of Thrombotic Events  
*Ji Zhang and Jason Crawford*

14.1 Background  
14.2 Pharmacology  
14.3 Structure–Activity Relationship (SAR)  
14.4 Pharmacokinetics and Drug Metabolism  
14.5 Efficacy and Safety  
14.6 Syntheses  
14.7 Compounds in Development: Apixaban and Otamixaban  
14.8 References  

Chapter 15. Endothelin Antagonists for the Treatment of Pulmonary Arterial Hypertension  
*David J. Edmonds*

15.1 Background  
15.2 Treatment of PAH  
15.3 Endothelin Antagonists  
15.4 Synthesis of Bosentan  
15.5 Synthesis of Sitaxsentan  
15.6 Synthesis of Ambrisentan  
15.7 Conclusion  
15.8 References
IV. Central Nervous System Diseases

Chapter 16. Varenicline (Chantix), An α4β2 Nicotinic Receptor Partial Agonist for Smoking Cessation

Jotham W. Coe, Frank R. Busch and Robert A. Singer

16.1 Background
16.2 Discovery Chemistry Program
16.3 Pharmacology
16.4 Pharmacokinetics and Drug Metabolism
16.5 Efficacy and Safety
16.6 Syntheses
16.7 References

Chapter 17. Donepezil, Rivastigmine, and Galantamine: Cholinesterase Inhibitors for Alzheimer Disease

Subas Sakyia and Kapil Karki

17.1 Background
17.2 Pharmacology
17.3 Structure–Activity Relationship (SAR)
17.4 Pharmacokinetics and Drug Metabolism
17.5 Efficacy and Safety
17.6 Synthesis of Donepezil
17.7 Synthesis of Rivastigmine
17.8 Synthesis of Galantamine
17.9 References

Chapter 18. Aprepitant (Emend): A NK1 Receptor Antagonist for the Treatment of Postchemotherapy Emesis

John A. Lowe III

18.1 Background
18.2 In Vitro Pharmacology and Structure–Activity Relationships
18.3 In Vivo Pharmacology
18.4 Pharmacokinetics and Drug Metabolism
18.5 Efficacy and Safety
18.6 Syntheses
18.7 References

Chapter 19. Armodafinil (Nuvigil): A Psychostimulant for the Treatment of Narcolepsy

Ji Zhang and Jason Crawford

19.1 Background
19.2 Pharmacology
19.3 Pharmacokinetics and Drug Metabolism
19.4 Efficacy and Safety
19.5 Synthesis
19.6 References
V. Miscellaneous

Chapter 20. Raloxifene (Evista): A Selective Estrogen Receptor Modulator (SERM)

Marta Piñeiro-Núñez

20.1 Background 309
20.2 Mechanism of Action 313
20.3 Pharmacokinetics and Drug Metabolism 313
20.4 Efficacy and Safety 314
20.5 Syntheses 315
20.6 References 325

Chapter 21. Latanoprost (Xalatan): A Prostanoid FP Agonist for Glaucoma

Sajiv K. Nair and Kevin E. Henegar

21.1 Background 329
21.2 Syntheses 331
21.3 References 337

Index 339