Contents

List of Contributors XI Preface XV A Personal Foreword XVII

1 Introduction 1 Andrew S. Bell and Spiros Liras

2	Toward a New Generation of PDE5 Inhibitors through Advances in Medicinal Chemistry 9
2.1	Dafydd R. Owen Introduction 9
2.2	The First-Generation Agents 10
2.3	PDE5 as a Mechanism and Alternative Indications Beyond MED
2.4	A Summary of PDE5 Chemotypes Reported Post-2010 11
2.5	Second-Generation PDE5 Inhibitors from Pfizer:
	Pyrazolopyrimidines 12
2.6	Second-Generation PDE5 Inhibitors from Pfizer:
	Pyridopyrazinones 18
2.7	Conclusions 25
	References 25
3	PDE4: New Structural Insights into the Regulatory Mechanism
	and Implications for the Design of Selective Inhibitors 29
	Jayvardhan Pandit
3.1	Introduction 29
3.2	Isoforms, Domain Organization, and Splice Variants 30
3.3	Structural Features of the Catalytic Site 31
3.4	Regulation of PDE4 Activity 32
3.5	Crystal Structure of Regulatory Domains of PDE4 33
3.6	UCR2 Interaction and Selectivity 38
3.7	Conclusions 39

۱v

11

References 40

VI Contents

4	PDE4: Recent Medicinal Chemistry Strategies to Mitigate Adverse
	Effects 45
	Etzer Darout, Elnaz Menhaji-Klotz, and Thomas A. Chappie
4.1	Introduction 45
4.2	Brief Summary of pan-PDE4 Inhibitors 46
4.2.1	Rolipram 47
4.2.2	Roflumilast 48
4.2.3	Cilomilast 48
4.2.4	Apremilast 49
4.3	PDE4 Strategies to Avoid Gastrointestinal Events 49
4.3.1	Allosteric Modulation 49
4.3.2	PDE4D Selectivity 53
4.3.3	Pfizer 53
4.3.4	Novartis 54
4.3.5	Merck-Frosst 54
4.3.6	GEBR-7b 55
4.3.7	PDE4B Selectivity 55
4.3.8	Asahi Kasei 56
4.3.9	GlaxoSmithKline 56
4.3.10	Pfizer 57
4.3.11	Tissue Targeting 57
4.3.12	Polypharmacology 58
4.3.13	Olanzapine Derivatives 58
4.4	Conclusions 59
	References 60
5	The Function, Enzyme Kinetics, Structural Biology, and Medicinal
	Chemistry of PDE10A 65
	Thomas A. Chappie and Patrick Verhoest
5.1	Enzymology and Protein Structure 66
5.2	Papaverine-Related PDE10A Inhibitors 69
5.3	MP-10/PF-2545920 Class of Inhibitors 72
5.4	PF-2545920/MP-Inspired Inhibitors 74
5.5	PF-2545920/Papaverine/Quinazoline Hybrid Series of Inhibitors 75
5.6	PET Ligand Development 77
5.7	Summary and Future 79
	References 79
6	The State of the Art in Selective PDE2A Inhibitor Design 83
	Christopher W. am Ende, Bethany L. Kormos, and John M. Humphrey
6.1	Introduction 83
6.2	Selective PDE2A Inhibitors 84
6.2.1	Bayer 84
6.2.2	Altana AG 85
6.2.3	Biotie Therapies 87

- 6.2.4 Boehringer Ingelheim 88
- 6.2.5 Janssen 89
- 6.2.6 Lundbeck 92
- 6.2.7 Merck 93
- 6.2.8 Neuro3d 95
- 6.2.9 Pfizer 95
- 6.3 Methods 100
- 6.4 Conclusions 100
 - References 101
- 7 Crystal Structures of Phosphodiesterase 9A and Insight into Inhibitor Discovery 105
 - Hengming Ke, Yousheng Wang, Yiqian Wan, and Hai-Bin Luo
- 7.1 Introduction 105
- 7.2 Subtle Asymmetry of the PDE9 Dimer in the Crystals 105
- 7.3 The Structure of the PDE9 Catalytic Domain 107
- 7.4 Interaction of Inhibitors with PDE9 108
- 7.5 Implication on Inhibitor Selectivity 110 References 114
- 8 PDEs as CNS Targets: PDE9 Inhibitors for Cognitive Deficit Diseases 117
 - Michelle M. Claffey, Christopher J. Helal, and Xinjun Hou
- 8.1 PDE9A Enzymology and Pharmacology 117
- 8.2 Crystal Structures of PDE9A Inhibitors 119
- 8.3 Medicinal Chemistry Efforts toward Identifying PDE9A Inhibitors for Treating Cognitive Disorders 120
- 8.3.1 Bayer 120
- 8.3.2 Pfizer 125
- 8.3.3 Boehringer Ingelheim 129
- 8.3.4 Sun Yat-Sen University, China 132
- 8.3.5 Envivo Pharmaceuticals 133
- 8.4 Analysis of CNS Desirability of PDE9A Inhibitors 135
- 8.5 Conclusions 135 References 137

9 Phosphodiesterase 8B 141

- Stephen W. Wright
- 9.1 Introduction 141
- 9.2 Identification 141
- 9.3 Properties 142
- 9.4 Expression and Tissue Distribution 143
- 9.5 Functions of PDE8B 143
- 9.5.1 Thyroid 144
- 9.5.2 Adrenal Gland 144

VIII Contents

9.5.3	Pancreatic Islets 144
9.6	Inhibitors and Potential Therapeutic Uses 145
	References 150
10	Selective New Small-Molecule Inhibitors of Phosphodiesterase 1 155
	John M. Humphrey
10.1	Introduction 155
10.2	PDE1 Enzymology 155
10.3	PDE1 Inhibitors 156
10.3.1	Non-Selective PDE1 Inhibitors 156
10.3.2	Selective PDE1 inhibitors 158
10.4	Conclusion 161
	References 163
11	Recent Advances in the Development of PDE7 Inhibitors 165 Nigel A. Swain and Rainer Gewald
11.1	Introduction 165
11.1	PDE7: Subtypes and Distribution 165
11.1.1	Rationale for PDE7 as a Therapeutic Target 166
11.1.2 11.2	Historical Development of PDE7 Inhibitors 166
11.2	Early Examples of Nonselective and Selective Lead Matter 166
11.2.1	
11.2.2	IO
11.2.5	Targeting PDE4/7 Dual Inhibitors168Recent Advances in the Discovery of PDE7 Inhibitors for Peripheral
11.5	Therapeutic Benefit 169
11.3.1	PDE7 Inhibitors for the Treatment of T Cell-Related Disorders 169
11.3.1.1	Developments in PDE7 Inhibitors for the Treatment of Airway-Related
11101111	Disorders 170
11.3.1.2	Developments in PDE7 Inhibitors for the Treatment of Nonairway-
	Related Disorders 171
11.3.1.3	Summary of T-Cell-Related Research 171
11.3.2	PDE7 Inhibitors for the Treatment of Neuropathic Pain 172
11.4	Recent Advances in the Discovery of PDE7 Inhibitors for CNS-Related
	Disorders 173
11.4.1	Creating PDE7 Inhibitors by Ligand-Based Virtual Screening
	Methods 173
11.4.2	Repositioning PDE7 Inhibitors Designed for the Treatment of
	Peripheral Diseases 176
11.5	Recent Advances in the Discovery of Dual PDE7 Inhibitors 178
11.5.1	Dual PDE4/7 Inhibitors 178
11.5.2	Dual PDE7/8 Inhibitors 180
11.6	Identifying Next-Generation PDE7 Inhibitors 181
11.6.1	Emerging Chemotypes as Novel PDE7 Inhibitors 181
11.6.2	Novel Methods to Identify PDE7 Inhibitors 182
11.6.2.1	Computational Methods to Identify New PDE7 Inhibitors 182

11.6.2.2 Fission Yeast-Based HTS to Identify New PDE7 Inhibitors 183
11.7 Summary 184 References 185

12 Inhibitors of Protozoan Phosphodiesterases as Potential Therapeutic Approaches for Tropical Diseases 191

Jennifer L. Woodring and Michael P. Pollastri

- 12.1 Introduction 191
- 12.2 Malaria 192
- 12.2.1 PfPDE Inhibition Studies 193
- 12.3 Chagas Disease 195
- 12.4 Leishmaniasis 197
- 12.5 Human African Trypanosomiasis 200
- 12.6 Conclusion 205
 - References 206

Index 211