SMALL MOLECULE MEDICINAL CHEMISTRY

Strategies and Technologies

Edited by

WERNGARD CZECHTIZKY PETER HAMLEY



CONTENTS

LI	IST OF CONTRIBUTORS	xiii	
	Introduction Werngard Czechtizky and Peter Hamley	1	
	ART I EXPLORING BIOLOGICAL SPACE: ACCESS TO NEW OLLECTIONS	11	
1	Elements for the Development of Strategies for Compound Library Enhancement <i>Edgar Jacoby</i>	13	
	 1.1 Introduction, 13 1.2 Chemical Space for Drug Discovery, 14 1.3 Molecular Properties for Drug Discovery, 17 1.4 Major Compound Classes, 21 1.5 Chemical Design Approaches to Expand Bioactive Chemical Space, 25 1.6 Conclusion, 28 Acknowledgments, 29 References, 29 		
2	The European Lead Factory Christopher Kallus, Jörg Hüser, Philip S. Jones, and Adam Nelson		
	 2.1 Introduction, 37 2.1.1 Background, 37 2.1.2 The European Lead Factory, 38 		

- 2.2 Building the Joint European Compound Library, 43
 - 2.2.1 Definition of Criteria and an Approach for the Review and Selection of Library Proposals, 46
 - 2.2.2 Collation, Review, and Selection of an Initial Wave of Library Proposals, 47
 - 2.2.3 A Web-Based Tool to Support the Collation, Review, and Selection of Proposals, 49
 - 2.2.4 Synthetic Validation of Library Proposals and Library Production, 49
- 2.3 Qualified Hit Generation, 54
 - 2.3.1 Capabilities of the ESC, 54
 - 2.3.2 Target Selection and Generation of Qualified Hits, 56
 - 2.3.3 Exploitation of Qualified Hit List, 58
- 2.4 Future Perspectives, 58
- Acknowledgments, 59

References, 59

3 Access to Compound Collections: New Business Models for Compound Acquisition and Sharing

Peter ten Holte

- 3.1 Introduction, 61
 - 3.1.1 Vertical Disintegration and the Quest for Innovation, 61
 - 3.1.2 Innovative Chemistry, 63
 - 3.1.3 Access to Supplementary Compound Collections, 63
- 3.2 Risk-Sharing Approaches, 64
 - 3.2.1 Overview, 64
 - 3.2.2 Blinded Screening, 65
 - 3.2.3 Follow-Up of Blinded Screening: Various Models, 65
- 3.3 Library Exchange, 69
 - 3.3.1 Partners with Different Scientific Interests, 70
 - 3.3.2 Partners with Similar Scientific Interests, 70
 - 3.3.3 Compound Selection: Use and Potential Risks, 71
- 3.4 Sharing Collections for External Screening, 72
 - 3.4.1 Rationale, 72
 - 3.4.2 Academic Drug Discovery Consortium (ADDC), 72
 - 3.4.3 EU-OPENSCREEN, 73
 - 3.4.4 NIH Roadmap, 73
- 3.5 Conclusion, 74

Acknowledgments, 74

References, 75

PART II EXPLORING BIOLOGICAL SPACE: ACCESS TO NEW CHEMISTRIES

4 New Advances in Diversity-Oriented Synthesis

Warren R. J. D. Galloway, Jamie E. Stokes, and David R. Spring

- 4.1 Introduction: Small Molecules and Biology, 79
- 4.2 The Need for Structural Diversity in Synthetic Small Molecule Screening Collections, 80

77

79

61

4.3 Diversity-Oriented Synthesis of New Structurally Diverse Compound Collections, 82

- 4.3.1 General Principles of Diversity-Oriented Synthesis, 82
- 4.3.2 Achieving Structural Diversity: The Importance of Scaffold Diversity, 83
- 4.3.3 Synthetic Principles in DOS, 83
- 4.3.4 Scaffold Diversity and Molecular Type, 86
- 4.3.5 Examples of DOS Campaigns, 86
- 4.4 Concluding Remarks, 97

References, 98

5 Solid-Phase Combinatorial Chemistry

Marcel Patek, Martin Smrcina, Eric Wegrzyniak, Victor Nikolaev, and Andres Mariscal

- 5.1 Introduction, 103
- 5.2 Chapter Outline, 104
- 5.3 Combinatorial Chemistry in Retrospect, 104
- 5.4 Foundations of Solid-Phase Synthesis of Combinatorial Chemistry, 107
 - 5.4.1 Ingredients of Solid-Phase Chemistry, 109
 - 5.4.2 Library Development and Production, 117
 - 5.4.3 Analytical Chemistry and Solid-Phase Synthesis of Libraries, 129
- 5.5 The Outcome of Tucson Combinatorial Chemistry at Sanofi, 132
 - 5.5.1 Overall Strategy, 132
 - 5.5.2 Drug Discovery Outcomes, 134
 - 5.5.3 Key Parameters of Combichem Productivity, 134
- 5.6 Conclusions and Outlook, 135

References, 136

6 Recent Advances in Multicomponent Reaction Chemistry: Applications in Small Molecule Drug Discovery

Christopher Hulme, Muhammad Ayaz, Guillermo Martinez-Ariza, Federico Medda, and Arthur Shaw

- 6.1 Introduction, 145
- 6.2 Classical Multi-Component Reactions (MCRs), 147
- 6.3 The Passerini Reaction (Mario Passerini, 1921), 147
- 6.4 Ugi Reaction, 147
 - 6.4.1 The Ugi-deprotect-cyclize (UDC) strategy, 152
 - 6.4.2 Bi-functional approach (BIFA), 153
 - 6.4.3 Miscellaneous Post-Ugi Condensations, 154
- 6.5 Van Leusen Reaction, 154
- 6.6 Petasis Reaction, 155
- 6.7 Groebke-Blackburn-Bienaymé (GBB) Reaction, 155
- 6.8 Recently Discovered Novel MCRs, 155
 - 6.8.1 Cyclic Anhydride-Based MCRs, 155
 - 6.8.2 1-Azadiene-Based MCRs, 156
 - 6.8.3 Recent IMCRs and Secondary Reactions, 157
 - 6.8.4 Miscellaneous MCRs, 159
- 6.9 Asymmetric MCRs, 159

145

189

6.10 Applications of MCRs in Medicinal Chemistry, 160

- 6.10.1 Kinase Inhibitors, 161
- 6.10.2 Protease Inhibitors, 163
- 6.10.3 Ion Channel Inhibitors, 165
- 6.10.4 Protein-Protein Interaction Inhibitors, 165
- 6.10.5 Tubulin Polymerization Inhibitors, 166
- 6.10.6 G-Protein-Coupled Receptors, 168
- 6.11 Summary, 171

References, 171

PART III SCREENING STRATEGIES

7		-	nal Techniques to Support Hit Triage	191
	Dougi	las B. Kit	chen and Hélène Y. Decornez	
	7.1	Lead F	Finding Process: Overview and Challenges, 191	
		7.1.1	The Need for Triage, 191	
		7.1.2	The Lead Generation Process, 191	
		7.1.3	Hit Triage: From Actives to Hits to Hit Series, 193	
		7.1.4	Challenges to Successful Lead Finding, 194	
		7.1.5	Frequent Hitters, 195	
		7.1.6	Implications of Human Decision-Making, 195	
	7.2	Chemi	cal Structure Analysis of Hit Lists, 196	
		7.2.1	Similarity-Based Clustering, 197	
		7.2.2	Scaffold-Based Clustering, 198	
		7.2.3	Application of Clustering Classification Methods, 201	
	7.3	Rules	and Filters, 201	
		7.3.1	Computational Descriptors for Property Assessment, 202	
		7.3.2	Lipophilicity and Other Physicochemical Descriptors, 205	
		7.3.3	Structural and Shape Descriptors, 205	
		7.3.4	Multiparameter Calculations: MPO and QED, 206	
		7.3.5	Frequent-Hitter Analysis, 207	
		7.3.6	Reactive Group Analysis, 209	
	7.4	Triage	Systems, 210	
	7.5	Ligano	l Efficiency Indices, 210	
	7.6	Hit Se	ries Analysis, 211	
		7.6.1	Latent Hit Series and Singletons, 211	
		7.6.2	Rapid Hit Exploration and Compound Set Enrichment, 211	
		7.6.3	SAR Analysis, 212	
		7.6.4	Data Volume, Integration, Retrieval, and Visualization, 213	
	7.7	Summ	ary, 214	
	Refer	ences, 2	214	
8	Fram	nent-Rs	ased Drug Discovery	221
~			see stug storter j	

Jean-Paul Renaud, Thomas Neumann, and Luc Van Hijfte

- 8.1 Introduction, 221
- 8.2 Fragment Libraries, 223

viii

- 8.3 Biophysical Screening Technologies, 223
 - 8.3.1 Surface Plasmon Resonance (SPR), 224
 - 8.3.2 Nuclear Magnetic Resonance (NMR), 231
 - 8.3.3 X-Ray Crystallography, 234
 - 8.3.4 Noncovalent Mass Spectrometry, 235
 - 8.3.5 Differential Scanning Fluorimetry (DSF), 237
 - 8.3.6 Biophysical Techniques for Fragment Screening against Membrane Proteins, 238
 - 8.3.7 Biophysical Techniques for Fragment Screening against PPIs, 238
- 8.4 Fragment Evolution Strategies, 239
- 8.5 FBDD Case Studies, 240
 - 8.5.1 Aurora Kinase Inhibitors, 240
 - 8.5.2 Tackling PPIs: Fragment-Based Discovery of Bromodomain Inhibitor Leads, 241
- 8.6 The Future, 243

References, 244

9 Virtual Screening

Karl-Heinz Baringhaus and Gerhard Hessler

- 9.1 Introduction, 251
 - 9.1.1 Goals of Virtual Screening, 252
- 9.2 Databases and Database Preparation, 254
- 9.3 Validation of the Virtual Screening Strategy, 256
- 9.4 Ligand-Based Virtual Screening, 258
 - 9.4.1 2D Approaches, 259
 - 9.4.2 3D Ligand-Based Approaches, 261
- 9.5 Structure-Based Virtual Screening, 263
- 9.6 Other Virtual Screening Applications, 266
- 9.7 Conclusion, 268

References, 269

10 Phenotypic Screening

Michelle Palmer

- 10.1 Introduction, 281
- 10.2 History and Past Successes, 282
- 10.3 Impact of Phenotypic Screening, 282
- 10.4 Model Systems for Phenotypic Assays, 285
 - 10.4.1 Cell Lines, 285
 - 10.4.2 Primary and Stem Cells, 285
 - 10.4.3 Cocultures, 286
 - 10.4.4 3D Cell Models, 287

10.5 Assays, 287

- 10.5.1 Assay Technologies, 287
- 10.5.2 Assay Development Considerations, 290
- 10.5.3 Example 1: Selective Killing of Breast Cancer Stem Cells, 291
- 10.5.4 Example 2: CFTR Potentiator Drug, 291

281

251

305

307

- 10.6 Deorphaning, 292
 - 10.6.1 Affinity-Based Proteomics, 292
 - 10.6.2 Genetic Profiling, 295
 - 10.6.3 Target Profiling, 296
 - 10.6.4 Comodifier Profiling, 296
 - 10.6.5 Target Engagement, 297
 - 10.6.6 Example 3: Elucidating MOA for a Regulator of Polyploidization, 297
- 10.7 Summary, 298

References, 299

PART IV TECHNOLOGIES FOR MEDICINAL CHEMISTRY OPTIMIZATION

11 Advances in the Understanding of Drug Properties in Medicinal Chemistry

Peter Hamley and Patrick Jimonet

- 11.1 Introduction, 307
- 11.2 Properties and Origins of Marketed Drugs, 308
 - 11.2.1 The Consistent Properties of Oral Drugs, 308
 - 11.2.2 The Changing Origins of Oral Drugs, 308
- 11.3 Drug Properties and Attrition in Clinical Development, 310
- 11.4 The Rule of Five, 312
 - 11.4.1 The Concept, 312
 - 11.4.2 Druggability, 313
- 11.5 The Concept of Lead-Likeness, 313
 - 11.5.1 The Consequences on Screening and Collections, 314
- 11.6 Influence of Drug Properties on Absorption, Distribution, Metabolism, Excretion, and Toxicity, 314
- 11.7 Building on the Ro5: New Guidelines for Compound Design, 316
 - 11.7.1 Ligand Efficiency, 316
 - 11.7.2 Ligand Lipophilicity Efficiency and Other Indices, 317
 - 11.7.3 Chemical Beauty, 318
- 11.8 Alternatives, Criticisms, and Exceptions, 318
- 11.9 Conclusions, 320
- References, 320

12 Recent Developments in Automated Solution Phase Library Production

Thomas C. Maier and Werngard Czechtizky

- 12.1 Introduction, 323
 - 12.1.1 Introduction and Definitions, 323
 - 12.1.2 Library Types, 324
 - 12.1.3 Chemotypes, 326

- 12.2 Library Production, 327
 - 12.2.1 The Library Production Process, 327
 - 12.2.2 Process Optimization, 330

12.3 New Technologies in Automated Liquid-Phase Library Synthesis, 334

- 12.3.1 Provision of Starting Materials: Automated Reagent Dispensaries, 334
- 12.3.2 Microwave, 335
- 12.3.3 Library Purification: Automated RP-HPLC and SFC as Orthogonal Methods, 336
- 12.4 Flow Chemistry and Gas-Phase Reactions, 342
 - 12.4.1 Reactive Gases in Flow, 344
- 12.5 Conclusion, 345

References, 345

13 ADME Profiling: An Introduction for the Medicinal Chemist

Katharina Mertsch, Martin Will, Werngard Czechtizky, Niels Griesang, Alexander Marker, and Jacob Olsen

- 13.1 Introduction, 353
- 13.2 Compound Profiling in H2L Optimization, 354
 - 13.2.1 Intestinal Absorption, 354
 - 13.2.2 Drug Metabolism and Inhibition of CYP450 Enzymes, 355
 - 13.2.3 Protein Binding, 356
 - 13.2.4 En Route to a Lead Series: In Vivo PK Studies, 358
- 13.3 Compound Profiling in Lead Optimization, 359
 - 13.3.1 Extended CYP Inhibition Studies, 359
 - 13.3.2 Mechanism-Based CYP Inhibition, 359
 - 13.3.3 Inhibition of Transport Proteins, 360
 - 13.3.4 Biopharmaceutical Classification of a Clinical Candidate (Classification of Potential Drugs into Biopharmaceutical Classification System or Biopharmaceutical Drug Disposition and Classification System), 360
- 13.4 Integration of Medicinal Chemistry, Biology, Physicochemical, and ADME Profiling: Strategies Toward Cycle Time Reductions, 362
 - 13.4.1 Planning Phase, 363
 - 13.4.2 Sample Preparation and Distribution, 364
 - 13.4.3 Compound QC, 365
 - 13.4.4 Determination of Physicochemical Properties, 367
 - 13.4.5 ADME Profiling: General Remarks, 369
 - 13.4.6 Metabolic Lability Profiling, 369
 - 13.4.7 Permeability Testing, 370
 - 13.4.8 CYP Inhibition Profiling, 372
- 13.5 Summary, 372

References, 373

PART V MEDICINAL CHEMISTRY BEYOND SMALL MOLECULES 379

The Role of Natural Products in Drug Discovery: Examples of Marketed Drugs			
edt and Karsten Siems			
Products and Natural Product Derivatives in Commercial Drugs, ead Optimization of Natural Product Hits, 397 udy 1: Taxol, 397 udy 2: Epothilone, 406 udy 3: Eribulin, 407 udy 4: Geldanamycin, 413 udy 5: Ingenol Mebutate (Picato), 417 ry, 422	381		
Peptidomimetics of α -Helical and β -Strand Protein Binding Epitopes Nina Bionda and Rudi Fasan			
-Protein Interactions as Therapeutic Targets, 431 mimetics of α-Helical Protein Binding Epitopes, 433 α-Helix-Mediated PPIs, 433 Side-Chain Cross-Linked α-Helices, 435 Hydrogen-Bond Surrogate-Stabilized α-Helices, 442 Other Type I α-Helix Peptidomimetics, 443 Type III α-Helix Peptidomimetics, 445 mimetics of β-Strand Protein Binding Epitopes, 446 β-Strand-Mediated PPIs, 446 Type I β-Strand Peptidomimetics, 447 Type III β-Strand Peptidomimetics, 449 sion, 452			
In Vivo Imaging of Drug Action Oliver Plettenburg and Matthias Löhn			
ction, 465 ew of Imaging Methods, 466 Fluorescence-Based Methods, 466 MRI, 470 CT, 470 PET/SPECT, 471 g of Therapeutic Effects, 476 Cancer, 476			
M C P g C C	IRI, 470 T, 470 ET/SPECT, 471 of Therapeutic Effects, 476		

- 16.3.3 CNS Disorders, 486
- 16.4 Conclusion and Outlook, 490

References, 491

INDEX