CONTENTS

Contributors xi
Preface xiii

17 Bioactive Molecules in Medicinal Plants: A Perspective on Their Therapeutic Action 1
S. C. Taneja and G. N. Qazi

17.1 Introduction, 1
17.2 Evolutionary Relationships Among Plants and Humans, 2
17.3 Traditional Wisdom, 3
17.4 Unique Libraries for Plants, 4
17.5 Drugs and Bioactive Molecules from Plants, 6
17.6 Synergism in Herbal Formulations, 36
17.7 Interactions Between Modern Drugs and Natural Products, 37
17.8 Bioavailability and Bioefficacy Enhancers, 38
17.9 Combination Therapies in Modern Drugs, 39
17.10 Role of Developments in Technologies and Analytical Tools, 40
  17.10.1 Developments in Separation Technologies, 40
  17.10.2 Developments in Combined Techniques and Advanced Technologies, 41
  17.10.3 Molecular Farming and Bioengineering of Medicinal Plants, 42
  17.10.4 High-Throughput Screening of Natural Products, 42
17.11 Herbal Medicine: The Best Possible Route to Health Care, 43
References, 44
## Natural Products as an Inspiration for the Discovery of New High-Throughput Chemical Synthesis Tools

Steven V. Ley, Ian R. Baxendale, Deborah A. Longbottom, and Rebecca M. Myers

18.1 Introduction, 51
18.2 Solid-Supported Reagents as Tools in Natural Product Synthesis, 52
18.3 Multistep Use of Supported Reagents in Natural Product Synthesis, 57
18.4 Conclusions, 85
References, 86

## Insulin Sensitizers: Emerging Therapeutics

Braj B. Lohray and Vidya B. Lohray

19.1 Introduction, 91
19.2 Therapeutic Interventions, 92
19.3 Discovery of Insulin Sensitizers, 92
19.4 Journey Toward New Drugs, 94
19.5 Conclusions, 116
References, 117

## Criteria for Industrial Readiness of Chiral Catalysis Technology for the Synthesis of Pharmaceuticals

Raymond McCague and Ian C. Lennon

20.1 Introduction, 121
20.2 Criteria for Technology Readiness, 122
20.3 Examples of Industrially Ready Chiral Catalytic Technologies and Their Application, 124
  20.3.1 Lipase Bioresolution: Ethyl 3-Amino-3-Phenylpropionate, 124
  20.3.2 Aminoacylase Bioresolution of N-Acylamino Acids, 126
  20.3.3 Asymmetric Hydrogenation of Prochiral Olefins by Rhodium–DuPhos Catalysts, 127
  20.3.4 Asymmetric Hydrogenation of Prochiral Ketones by Ruthenium–Biphosphine–Diamine Catalysts, 129
  20.3.5 Asymmetric Hydroformylation with Rhodium–Phosphite Catalysts, 132
  20.3.6 Asymmetric Allylic Substitution with Palladium-Based Catalysts, 133
20.4 How Industrially Ready Technology Can Deliver Commercial Advantages, 136
20.5 Conclusions, 138
References, 138

## Enantioselective Synthesis of Propargyl Alcohols as Multifunctional Synthons

J. S. Yadav and S. Chandrasekhar

21.1 Introduction, 141
21.2 Asymmetric Reduction of Prochiral α, β-Alkynyl Ketones, 142
21.3 Addition of Acetylenic Anion to Carbonyl Carbon, 148
21.4 Desymmetrization and Enzymatic Strategies for Chiral Propargyl Alcohol Synthesis, 155
21.5 β-Elimination Strategy and Miscellaneous Approaches, 157
21.6 Conclusions, 159
References, 159

22 Carbohydrates: From Chirons to Mimics 161
G. V. M. Sharma and Palakodety Radha Krishna
22.1 Introduction, 161
22.2 Synthetic Strategies for C-Glycosides, 162
22.3 Synthetic Strategies for Carbon-Linked Disaccharides and Pseudosaccharides, 168
References, 178

23 Meeting the Challenges of Process Development and Scale-up of Active Pharmaceutical Ingredients 181
Yatendra Kumar and B. Vijayaraghavan
23.1 Introduction, 181
23.1.1 Drug Development in the Pharmaceutical Industry, 181
23.1.2 Challenges in Developing and Scaling Up Chemical Processes, 182
23.2 Process Development Cycle, 183
23.2.1 Stage I. Literature Survey and Analysis: Preparing the Blueprint, 184
23.2.2 Stage II. Process Development: Laying the Foundation, 189
23.2.3 Stage III. Process Optimization: Constructing the Building Brick by Brick, 192
23.2.4 Stage IV. Process Validation: Finishing Touches—Grinding and Polishing, 195
23.2.5 Stage V. Process Scale-up: The Moment of Truth, 196
23.3 Conclusions, 198
References, 198

24 Importance of Polymorphs and Salts in the Pharmaceutical Industry 201
Bipin Pandey, Vidya B. Lohray, and Braj B. Lohray
24.1 Introduction, 201
24.2 Drug Discovery and Development, 202
24.3 Salt Selection, 204
24.4 Pseudopolymorphs, 206
24.4.1 Hydrates, 206
24.4.2 Solvates, 207
24.4.3 Amorphous Solids, 208
24.5 Analytical Tools, 208
24.6 Process Development, 210
24.7 Formulation Development, 212
24.8 Regulatory Concerns, 213
CONTENTS

24.9 Patent Implications, 213
24.10 Predictions and Uncertainties, 214
24.11 Conclusions, 215
References, 216

25 Role of Outsourcing in Drug Manufacture
Peter Pollak
25.1 Introduction, 219
25.2 Outsourcing in the Pharmaceutical Industry, 220
   25.2.1 Outsourcing of Chemical Manufacturing, 222
   25.2.2 Outsourcing of Research and Development, 231
References, 232

26 Regulation-Driven Process Chemistry
Shrikant V. Kulkarni
26.1 Introduction, 233
26.2 Chemical Industry Regulatory Guidelines, 233
26.3 Manufacturing Techniques in Process Chemistry, 237
26.4 Effects of Pesticide Industry Regulation, 239
26.5 Efforts at Denitrification, 241
26.6 Evolution to Green Chemistry, 247
References, 248

27 Chemical Process Scale-up Tools: Mixing Calculations, Statistical Design of Experiments, and Automated Laboratory Reactors
Andrei A. Zlota
27.1 Chemical Process Scale-up Challenges, 251
27.2 Case Study: Development of an Active Pharmaceutical Ingredient Crystallization Process, 253
27.3 Case Study: Determination of a Scale-up Factor for the Bourne III Reactive System, 256
27.4 Conclusions, 261
References and Notes, 262

28 Library Quality Metrics
Richard L. Wife and Johan Tijhuis
28.1 Drug Discovery and Development, 265
28.2 Compound Libraries, 267
28.3 Library Metrics, 268
   28.3.1 Chemical Structure, 268
   28.3.2 Druglikeness, 269
   28.3.3 Novelty, 270
   28.3.4 Diversity, 272
   28.3.5 Numbers and Costs, 273
   28.3.6 Analogs, 274
28.3.7 Resupply, 275
28.3.8 Compound Purity, 275
28.3.9 Compound Stability, 276
28.3.10 Compound Solubility, 276
28.3.11 Serendipity, 276

28.4 Conclusions, 277

29 Tying a GABA from Copenhagen to Chicago: The Chemistry of Tiagabine
Mukund S. Chorghade, Mahendra N. Deshpande, and Richard J. Pariza

29.1 Introduction, 279
29.2 Synthesis of Symmetrical Analogs: Tiagabine, 285
29.3 Synthesis of Unsymmetrical Analogs: Desmethyltiagabine, 288
29.3.1 Syntheses of Regioisomers of Tiagabine, 291
29.3.2 Human Metabolite of Tiagabine: 5-Hydroxytiagabine, 292
29.4 Attempted Biomimetic Synthesis of 5-Hydroxytiagabine, 296
29.5 Oxidative Degradation Products of Tiagabine, 298
29.5.1 Dihydroxytiagabine, 298
29.5.2 Ketotiaabine, 299
29.6 Metalloporphyrins as Chemical Mimics of Cytochrome P450
   Systems, 301
29.6.1 Oxometalloporphyrins, 302
29.6.2 Synthesis of the Sterically Protected and Electronically
   Activated Metalloporphyrins, 303
29.6.3 Application of the Methodology to Selected Drugs, 303

References, 306

30 Building Contract Research Businesses Based on Integration of Basic and Applied Research
Mukund S. Chorghade, Mukund K. Gurjar, C. V. Ramana, and Sreenivas Punna

30.1 Introduction, 309
30.2 Solving Real-World Problems, 312
30.2.1 Synthesis of β-Blockers, 315
30.2.2 Ring-Closing Metatheses as a Pathway to Chiral Compounds, 319
30.3 Synthesis of Pharmaceutically Relevant Chiral Tetrahydrofurans, 323
30.3.1 Discovery Route, 325
30.3.2 Alternative Strategies for Synthesis of Compounds 130 to 133 Based on C-Alkynyl Furan Derivatives, 334
30.4 Drugs for the Treatment of Skin Disorders, 339
30.4.1 Discovery Synthesis of Compound 229, 340
30.4.2 Process Innovation for Compound 229: Systematic Investigation, 341
30.4.3 Alternative Routes for Compound 229, 346
30.5 Conclusions, 350

References, 350
31 Principles and Practice of Clinical Drug Development

Colin Scott

31.1 Introduction, 355
31.2 History of Ethical Medical Research, 356
31.3 History of the Regulation of Medical Research, 360
31.4 Preclinical Development, 364
31.5 Clinical Development, 369
31.6 Conclusions, 374

Index