Contents

Foreword    VII
Preface    XXI
About the Editor    XXV
List of Contributors    XXVII

1  An Overview    1
   Goutam Brahmachari

2  Use of Chemical Genomics to Investigate the Mechanism of Action for Inhibitory Bioactive Natural Compounds    9
   Daniel Burnside, Houman Motesharieh, Imelda G. Marquez, Mohsen Hooshyar, Bahram Samanfar, Kristina Shostak, Katayoun Omidi, Harry E. Peery, Myron L. Smith, and Ashkan Golshani
   2.1  Introduction: Antibiotic Resistance and the Use of Natural Products as a Source for Novel Antimicrobials    9
   2.2  Chemical Genetics and Genomics    10
   2.3  Development of GDA Technology    11
       2.3.1  The Use of Gene Deletion Arrays (GDAs) to Investigate MOA    12
       2.3.2  Chemical Genetic Interactions    12
       2.3.3  Quantifying Genetic and Chemical Genetic Interactions    14
       2.3.4  Data Analysis    15
       2.3.5  Platforms for Chemical Genomic GDA Studies    17
       2.3.6  Why Screen Natural Products in GDAs?    19
       2.3.7  Successful Applications of GDA Technology    21
   2.4  Concluding Remarks    22
   Abbreviations    24
   References    24
3 High-Throughput Drug Screening Based on Cancer Signaling in Natural Product Screening 33
Xinxin Zhang, Yuping Du, and Jinbo Yang
3.1 Introduction 33
3.2 Cancer Signaling Pathways with Their Own Drug Screening Assays in HTS 35
3.2.1 β-Galactosidase Enzyme Complementation Assays for EGFR Signaling Drug Screening 35
3.2.2 Fluorescence Superquenching Assays for PI3Ks Signaling Drug Screening 35
3.2.3 TOP Flash Reporter Gene Assays for Wnt Signaling Drug Screening 36
3.2.4 Luciferase Reporter Gene Assays for STATs Signaling Drug Screening 37
3.3 Concluding Remarks 37
Abbreviations 38
References 38

4 Immunosuppressants: Remarkable Microbial Products 43
Preeti Vaishnav, Young J. Yoo, Yeo J. Yoon, and Arnold L. Demain
4.1 Introduction 43
4.2 Discovery 44
4.3 Mode of Action 47
4.4 Biosynthesis 49
4.4.1 Acetate, Propionate, Butyrate, Methionine, and Valine as Precursors of the Macrolide Rings of Sirolimus, Ascomycin, and Tacrolimus 49
4.4.2 Pipecolate Moiety of the Macrolide Ring of Sirolimus, Ascomycin, and Tacrolimus 52
4.4.3 The Final Step in Biosynthesis of Ascomycins and Tacrolimus 55
4.4.4 Formation of the Substituted Cyclohexyl Moiety of Sirolimus, Tacrolimus, and Ascomycins 58
4.4.5 Biosynthesis of Cyclosporin 61
4.5 Genetics and Strain Improvement 63
4.6 Fermentation and Nutritional Studies 65
4.7 Other Activities of Immunosuppressants 69
4.8 Concluding Remarks 71
Acknowledgments 72
References 72
5 Activators and Inhibitors of ADAM-10 for Management of Cancer and Alzheimer’s Disease 83
Prajakta Kulkarni, Manas K. Haldar, and Sanku Mallik
5.1 Introduction to ADAM Family of Enzymes 83
5.2 ADAM-10 Structure and Physiological Roles 85
5.3 Pathological Significance 85
5.3.1 Modulating ADAM Activity in Neurodegeneration 85
5.3.2 ADAM-10 in Cancer Pathology 86
5.4 ADAM-10 as Potential Drug Target 87
5.5 Synthetic Inhibitors of ADAM-10 88
5.6 Natural Products as Activators and Inhibitors for ADAM-10 92
5.7 Natural Products as ADAM-10 Activators 93
5.7.1 Ginsenoside R 94
5.7.2 Curcuma longa 94
5.7.3 Ginkgo biloba 95
5.7.4 Green Tea 95
5.8 Natural Products as ADAM-10 Inhibitors 96
5.8.1 Triptolide 96
5.8.1.1 Novel Derivatives and Carriers of Triptolide 98
5.9 Concluding Remarks 99
Abbreviations 99
References 99

6 Structure and Biological Activity of Polyether Ionophores and Their Semisynthetic Derivatives 107
Michał Antoszczak, Jacek Rutkowski, and Adam Huczyński
6.1 Introduction 107
6.2 Structures of Polyether Ionophores and Their Derivatives 108
6.2.1 Monensin and Its Derivatives 112
6.2.2 Salinomycin and Its Derivatives 117
6.2.3 Lasalocid Acid A and Its Derivatives 118
6.2.4 Other Polyether Ionophores 125
6.2.4.1 Ionophores with Monensin Skeleton 125
6.2.4.2 Polyether Ionophores with Dianemycin Skeleton 126
6.3 Chemical Properties of Polyether Ionophores and Their Derivatives 130
6.3.1 Complexes of Ionophores with Metal Cations 130
6.3.2 Mechanism of Cation Transport 132
6.4 Biological Activity 133
Contents

6.4.1 Antibacterial Activity of Polyether Antibiotics and Their Derivatives 135
6.4.2 Antifungal Activity of Polyether Antibiotics and Their Derivatives 140
6.4.3 Antiparasitic Activity of Polyether Antibiotics and Their Derivatives 141
6.4.4 Antiviral Activity of Polyether Antibiotics 144
6.4.5 Anticancer Activity of Polyether Antibiotics and Their Derivatives 145
6.5 Concluding Remarks 153

Abbreviations 154
References 155

7 Bioactive Flavaglines: Synthesis and Pharmacology 171
Christine Basmadjian, Qian Zhao, Armand de Gramont, Maria Serova, Sandrine Faivre, Eric Raymond, Stephan Vagner, Caroline Robert, Canan G. Nebigil, and Laurent Désaubry

7.1 Introduction 171
7.2 Biosynthetic Aspects 172
7.3 Synthesis of Flavaglines 174
7.3.1 Chemical Syntheses 174
7.3.2 Biomimetic Synthesis of Flavaglines 179
7.3.3 Synthesis of Silvestrol (6) 182
7.4 Pharmacological Properties of Flavaglines 184
7.4.1 Anticancer Activity 184
7.4.2 Anti-inflammatory and Immunosuppressant Activities 190
7.4.3 Cytoprotective Activity 190
7.4.4 Antimalarial Activities 191
7.5 Structure–Activity Relationships (SARs) 192
7.6 Concluding Remarks 192
Abbreviations 193
References 194

8 Beneficial Effect of Naturally Occurring Antioxidants against Oxidative Stress–Mediated Organ Dysfunctions 199
Pabitra B. Pal, Shatadal Ghosh, and Parames C. Sil

8.1 Introduction 199
8.2 Oxidative Stress and Antioxidants 200
8.2.1 Mangiferin and Its Beneficial Properties 200
8.2.1.1 Antioxidant Activity of Mangiferin 200
8.2.1.2 Anti-inflammatory Activity of Mangiferin 201
8.2.1.3 Immunomodulatory Effect 202
8.2.1.4 Antidiabetic Activity 203

Abbreviations 204
References 205
8.2.1.5 Iron Complexing Activity of Mangiferin 205
8.2.1.6 Mangiferin Protects against Mercury-Induced Toxicity 205
8.2.1.7 Mangiferin Protects Murine Liver against Pb(II)–Induced Hepatic Damage 206
8.2.2 Arjunolic Acid 207
8.2.2.1 Cardioprotective Effects of Arjunolic Acid 208
8.2.2.2 Antidiabetic Activity 211
8.2.2.3 Arjunolic Acid Protects Organs from Acetaminophen (APAP)-Induced Toxicity 211
8.2.2.4 Arjunolic Acid Protects Liver from Sodium Fluoride-Induced Toxicity 212
8.2.2.5 Protection against Arsenic-Induced Toxicity 212
8.2.2.6 Mechanism of Action of Arjunolic Acid 214
8.2.3 Baicalein 214
8.2.3.1 Baicalein Protects Human Melanocytes from H₂O₂-Induced Apoptosis 215
8.2.3.2 Protection against Doxorubicin-Induced Cardiotoxicity 215
8.2.4 Silymarin 216
8.2.4.1 Physicochemical and Pharmacokinetic Properties of Silymarin 216
8.2.4.2 Metabolism of Silymarin 217
8.2.4.3 Antioxidant Activity of Silymarin 217
8.2.4.4 Protective Effect of Silydianin against Reactive Oxygen Species 219
8.2.4.5 Diabetes and Silymarin 219
8.2.4.6 Silibinin Protects H9c2 Cardiac Cells from Oxidative Stress 219
8.2.4.7 Silymarin Protects Liver from Doxorubicin-Induced Oxidative Damage 220
8.2.4.8 Silymarin and Hepatoprotection 220
8.2.4.9 Stimulation of Liver Regeneration 221
8.2.5 Curcumin 221
8.2.5.1 Chemical Composition of Turmeric 222
8.2.5.2 Metabolism of Curcumin 222
8.2.5.3 Antioxidant Activity of Curcumin 222
8.2.5.4 Diabetes and Curcumin 225
8.2.5.5 Efficacy of Biodegradable Curcumin Nanoparticles in Delaying Cataract in Diabetic Rat Model 226
8.3 Concluding Remarks 227
9 Isoquinoline Alkaloids and Their Analogs: Nucleic Acid and Protein Binding Aspects, and Therapeutic Potential for Drug Design 241
9.1 Introduction 241
9.2 Isoquinoline Alkaloids and Their Analogs 243
  9.2.1 Berberine 243
    9.2.1.1 Interaction of Berberine with Deoxyribonucleic Acids 244
    9.2.1.2 DNA Binding of Berberine Analogs 245
    9.2.1.3 Binding of Berberine and Analogs to Polymorphic DNA Conformations 248
    9.2.1.4 Interaction of Berberine and Analogs with Ribonucleic Acids 253
    9.2.1.5 Interaction of Berberine and Analogs with Proteins 258
  9.2.2 Palmatine 260
    9.2.2.1 Interaction of Palmatine and Analogs to Deoxyribonucleic Acids 261
    9.2.2.2 Interaction of Palmatine with RNA 262
    9.2.2.3 Interactions of Palmatine with Proteins 264
  9.2.3 OtherIsoquinoline Alkaloids: Jatrorrhizine, Copticine, and Analogs – DNA/RNA and Protein Interactions 266
9.3 Concluding Remarks 267
Acknowledgments 268
Abbreviations 268
References 269

10 The Potential of Peptides and depsipeptides from Terrestrial and Marine Organisms in the Fight against Human Protozoan Diseases 279
Jean Fotie
  10.1 Introduction 279
  10.2 Antiprotozoan Peptides and depsipeptides of Natural Origin and Their Synthetic Analogs 281
    10.2.1 Apicidins 281
    10.2.2 Almiramides and Dragonamides 282
    10.2.3 Balgacyclamides 285
    10.2.4 Beauvericins and Allobeauvericin 286
    10.2.5 Aerucyclamides 286
    10.2.6 Chondramides and Jaspamides 288
    10.2.7 Enniatins and Beauvenniatins 289
    10.2.8 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290
    10.2.9 Hirsutatins and Hirsutellides 291
    10.2.10 Alamethicin 292
    10.2.11 Gramicidins 293
    10.2.12 Kahalalides 294
    10.2.13 Lagunamides 295
    10.2.14 Paecilodepsipeptides 295
    10.2.15 Pullularins 296
    10.2.16 Szentiamide 297
10.2.17 Venturamides 297
10.2.18 Viridamides 298
10.2.19 Antiamoebin I 299
10.2.20 Efrapeptins 299
10.2.21 Valinomycin 300
10.2.22 Cyclosporins 300
10.2.23 Cyclolinopeptides 301
10.2.24 Cycloaspeptides 302
10.2.25 Mollamides 302
10.2.26 Tsushimycin 303
10.2.27 Leucinostatins 304
10.2.28 Cardinalisamides 304
10.2.29 Symplocamide A 305
10.2.30 Xenobactin 305
10.3 Concluding Remarks 306
Abbreviations 307
References 307

11 Sesquiterpene Lactones: A Versatile Class of Structurally Diverse Natural Products and Their Semisynthetic Analogs as Potential Anticancer Agents 321
Devdutt Chaturvedi, Parmesh Kumar Dwivedi, and Mamta Mishra

11.1 Introduction: Structural Features and Natural Distribution 321
11.2 Anticancer Activity of Sesquiterpenes Lactones 323
11.2.1 Costunolide and Analogs 324
11.2.2 Parthenolide and Analogs 328
11.2.3 Helenalin and Analogs 331
11.2.4 Artemisinin and Its Derivatives 332
11.2.5 Tourneforin and Its Derivatives 333
11.2.6 Eupalinin 333
11.2.7 Inuviscolide and Related Compounds 334
11.2.8 Japonicones 335
11.2.9 Isoalantolactone and Related Compounds 335
11.2.10 6-O-Angeloylenolin 336
11.2.11 Miscellaneous STLs Under Different Classes 336
11.2.11.1 Guianolides 336
11.2.11.2 Pseudoguaianolides 339
11.2.11.3 Eudesmanolides 339
11.2.11.4 Germacranolide 340
11.2.11.5 Other Anticancer Sesquiterpene Lactones 340
11.3 Structure–Activity Relationships (SARs) of Sesquiterpenes Lactones 340
## Contents

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4</td>
<td>Concluding Remarks</td>
<td>341</td>
</tr>
<tr>
<td></td>
<td>Acknowledgments</td>
<td>342</td>
</tr>
<tr>
<td></td>
<td>Abbreviations</td>
<td>342</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>342</td>
</tr>
<tr>
<td>12</td>
<td>Naturally Occurring Calanolides: Chemistry and Biology</td>
<td>349</td>
</tr>
<tr>
<td></td>
<td>Goutam Brahmachari</td>
<td></td>
</tr>
<tr>
<td>12.1</td>
<td>Introduction</td>
<td>349</td>
</tr>
<tr>
<td>12.2</td>
<td>Naturally Occurring Calanolides: Structures and Physical Properties</td>
<td>350</td>
</tr>
<tr>
<td>12.3</td>
<td>Anti-HIV and Antituberculosis Potential of Calanolides</td>
<td>350</td>
</tr>
<tr>
<td>12.3.1</td>
<td>Anti-HIV Potential of Calanolides</td>
<td>350</td>
</tr>
<tr>
<td>12.3.2</td>
<td>Studies on Structure–Activity Relationships (SARs) of Calanolides</td>
<td>355</td>
</tr>
<tr>
<td>12.3.3</td>
<td>Antituberculosis Potential of Calanolides and Related Derivatives</td>
<td>357</td>
</tr>
<tr>
<td>12.4</td>
<td>Total Syntheses of Calanolides</td>
<td>360</td>
</tr>
<tr>
<td>12.5</td>
<td>Concluding Remarks</td>
<td>369</td>
</tr>
<tr>
<td></td>
<td>Acknowledgment and Disclosure</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td>Abbreviations</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>371</td>
</tr>
<tr>
<td>13</td>
<td>Selective Estrogen Receptor Modulators (SERMs) from Plants</td>
<td>375</td>
</tr>
<tr>
<td></td>
<td>Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan</td>
<td></td>
</tr>
<tr>
<td>13.1</td>
<td>Introduction</td>
<td>375</td>
</tr>
<tr>
<td>13.2</td>
<td>Structure of Estrogen Receptor</td>
<td>376</td>
</tr>
<tr>
<td>13.3</td>
<td>Estrogen Receptor Signaling</td>
<td>377</td>
</tr>
<tr>
<td>13.4</td>
<td>Selective Estrogen Receptor Modulators from Plants</td>
<td>379</td>
</tr>
<tr>
<td>13.5</td>
<td>Molecular Basis of the Distinct SERM Action</td>
<td>381</td>
</tr>
<tr>
<td>13.6</td>
<td>SERMs in the Treatment of Estrogen-Mediated Cancers</td>
<td>383</td>
</tr>
<tr>
<td>13.7</td>
<td>Concluding Remarks</td>
<td>383</td>
</tr>
<tr>
<td></td>
<td>Abbreviations</td>
<td>384</td>
</tr>
<tr>
<td></td>
<td>References</td>
<td>384</td>
</tr>
<tr>
<td>14</td>
<td>Introduction to the Biosynthesis and Biological Activities of Phenylpropanoids</td>
<td>387</td>
</tr>
<tr>
<td></td>
<td>Luzia V. Modolo, Cristiane J. da Silva, Fernanda G. da Silva, Leonardo da Silva Neto, and Ângelo de Fátima</td>
<td></td>
</tr>
<tr>
<td>14.1</td>
<td>Introduction</td>
<td>387</td>
</tr>
<tr>
<td>14.2</td>
<td>Biosynthesis of Phenylpropanoids</td>
<td>387</td>
</tr>
</tbody>
</table>
14.3 Some Phenylpropanoid Subclasses 392
14.3.1 Flavonoids 392
14.3.1.1 Function in Plants 392
14.3.1.2 Pharmacological Properties 393
14.3.2 Coumarins 395
14.3.2.1 Function in Plants 395
14.3.2.2 Pharmacological Properties 396
14.3.3 Stilbenes 398
14.3.3.1 Function in Plants 398
14.3.3.2 Pharmacological Properties 399

14.4 Concluding Remarks 400
Acknowledgments 400
Abbreviations 400
References 401

15 Neuropeptides: Active Neuromodulators Involved in the Pathophysiology of Suicidal Behavior and Major Affective Disorders 409
Gianluca Serafini, Daniel Lindqvist, Lena Brundin, Yogesh Dwivedi, Paolo Girardi, and Mario Amore

15.1 Introduction 409
15.2 Methods 410
15.3 Involvement of Neuropeptides in the Pathophysiology of Suicidal Behavior and Major Affective Disorders 411
15.3.1 Corticotropin-Releasing Factor 411
15.3.2 Arginine Vasopressin 412
15.3.3 Oxytocin 413
15.3.4 Galanin 415
15.3.5 Tachykinins 415
15.3.6 Neuropeptide Y 418
15.3.7 Cholecystokinin 418
15.3.8 Dynorphins 420
15.3.9 Orexin 420
15.3.10 Neurotensin 423
15.3.11 Nociceptin 424
15.3.12 Melanin-Concentrating Hormone 424
15.3.13 Neuropeptide S 425
15.4 The Association between Neuropeptides, Suicidality, and Major Affective Disorders 426
15.5 Discussion of the Main Findings 429
15.6 Concluding Remarks 431
Abbreviations 432
References 433