

## Contents

	<b>Foreword</b>	<i>VII</i>
	<b>Preface</b>	<i>XXI</i>
	<b>About the Editor</b>	<i>XXV</i>
	<b>List of Contributors</b>	<i>XXVII</i>
<b>1</b>	<b>An Overview</b>	<i>1</i>
	<i>Goutam Brahmachari</i>	
<b>2</b>	<b>Use of Chemical Genomics to Investigate the Mechanism of Action for Inhibitory Bioactive Natural Compounds</b>	<i>9</i>
	<i>Daniel Burnside, Houman Moteshareie, Imelda G. Marquez, Mohsen Hooshyar, Bahram Samanfar, Kristina Shostak, Katayoun Omid, Harry E. Peery, Myron L. Smith, and Ashkan Golshani</i>	
<b>2.1</b>	<b>Introduction: Antibiotic Resistance and the Use of Natural Products as a Source for Novel Antimicrobials</b>	<i>9</i>
<b>2.2</b>	<b>Chemical Genetics and Genomics</b>	<i>10</i>
<b>2.3</b>	<b>Development of GDA Technology</b>	<i>11</i>
<b>2.3.1</b>	<b>The Use of Gene Deletion Arrays (GDAs) to Investigate MOA</b>	<i>12</i>
<b>2.3.2</b>	<b>Chemical Genetic Interactions</b>	<i>12</i>
<b>2.3.3</b>	<b>Quantifying Genetic and Chemical Genetic Interactions</b>	<i>14</i>
<b>2.3.4</b>	<b>Data Analysis</b>	<i>15</i>
<b>2.3.5</b>	<b>Platforms for Chemical Genomic GDA Studies</b>	<i>17</i>
<b>2.3.6</b>	<b>Why Screen Natural Products in GDAs?</b>	<i>19</i>
<b>2.3.7</b>	<b>Successful Applications of GDA Technology</b>	<i>21</i>
<b>2.4</b>	<b>Concluding Remarks</b>	<i>22</i>
	<b>Abbreviations</b>	<i>24</i>
	<b>References</b>	<i>24</i>

<b>3</b>	<b>High-Throughput Drug Screening Based on Cancer Signaling in Natural Product Screening</b> 33 <i>Xinxin Zhang, Yuping Du, and Jinbo Yang</i>
3.1	Introduction 33
3.2	Cancer Signaling Pathways with Their Own Drug Screening Assays in HTS 35
3.2.1	$\beta$ -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
<b>4</b>	<b>Immunosuppressants: Remarkable Microbial Products</b> 43 <i>Preeti Vaishnav, Young J. Yoo, Yeo J. Yoon, and Arnold L. Demain</i>
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	Pipicolate 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	<b>Activators and Inhibitors of ADAM-10 for Management of Cancer and Alzheimer's Disease 83</b> <i>Prajakta Kulkarni, Manas K. Halder, and Sanku Mallik</i>
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	<i>Curcuma longa</i> 94
5.7.3	<i>Ginkgo biloba</i> 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	<b>Structure and Biological Activity of Polyether Ionophores and Their Semisynthetic Derivatives 107</b> <i>Michał Antoszczak, Jacek Rutkowski, and Adam Huczyński</i>
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

- 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

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 H <sub>2</sub> O <sub>2</sub> -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
	Abbreviations	227
	References	228
9	<b>Isoquinoline Alkaloids and Their Analogs: Nucleic Acid and Protein Binding Aspects, and Therapeutic Potential for Drug Design</b>	241
	<i>Gopinatha S. Kumar</i>	
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	Other Isoquinoline Alkaloids: Jatrorrhizine, Copticine, and Analogs – DNA/RNA and Protein Interactions	266
9.3	Concluding Remarks	267
	Acknowledgments	268
	Abbreviations	268
	References	269
<b>10</b>	<b>The Potential of Peptides and Depsipeptides from Terrestrial and Marine Organisms in the Fight against Human Protozoan Diseases</b>	<b>279</b>
	<i>Jean Fotie</i>	
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 Allobauvericin	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
<b>11</b>	<b>Sesquiterpene Lactones: A Versatile Class of Structurally Diverse Natural Products and Their Semisynthetic Analogs as Potential Anticancer Agents</b>	<b>321</b>
	<i>Devdutt Chaturvedi, Parmesh Kumar Dwivedi, and Mamta Mishra</i>	
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	Tournefortin 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	Guaianolides	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

11.4	Concluding Remarks	341
	Acknowledgments	342
	Abbreviations	342
	References	342
12	<b>Naturally Occurring Calanolides: Chemistry and Biology</b>	349
	<i>Goutam Brahmachari</i>	
12.1	Introduction	349
12.2	Naturally Occurring Calanolides: Structures and Physical Properties	350
12.3	Anti-HIV and Antituberculosis Potential of Calanolides	350
12.3.1	Anti-HIV Potential of Calanolides	350
12.3.2	Studies on Structure–Activity Relationships (SARs) of Calanolides	355
12.3.3	Antituberculosis Potential of Calanolides and Related Derivatives	357
12.4	Total Syntheses of Calanolides	360
12.5	Concluding Remarks	369
	Acknowledgment and Disclosure	370
	Abbreviations	370
	References	371
13	<b>Selective Estrogen Receptor Modulators (SERMs) from Plants</b>	375
	<i>Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan</i>	
13.1	Introduction	375
13.2	Structure of Estrogen Receptor	376
13.3	Estrogen Receptor Signaling	377
13.4	Selective Estrogen Receptor Modulators from Plants	379
13.5	Molecular Basis of the Distinct SERM Action	381
13.6	SERMs in the Treatment of Estrogen-Mediated Cancers	383
13.7	Concluding Remarks	383
	Abbreviations	384
	References	384
14	<b>Introduction to the Biosynthesis and Biological Activities of Phenylpropanoids</b>	387
	<i>Luzia V. Modolo, Cristiane J. da Silva, Fernanda G. da Silva, Leonardo da Silva Neto, and Ângelo de Fátima</i>	
14.1	Introduction	387
14.2	Biosynthesis of Phenylpropanoids	387



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

16	<b>From Marine Organism to Potential Drug: Using Innovative Techniques to Identify and Characterize Novel Compounds – a Bottom-Up Approach</b> 443 <i>A. Jonathan Singh, Jessica J. Field, Paul H. Atkinson, Peter T. Northcote, and John H. Miller</i>
16.1	Introduction 443
16.2	Structural Screening Approach 445
16.2.1	Case Study 1: Colensolide from <i>Osmundaria colensoi</i> 448
16.2.2	Case Study 2: Zampanolide from <i>Cacospongia mycofijiensis</i> 449
16.3	Testing for Bioactivity by Screening in Mammalian Cells 452
16.4	Chemical Genetics and Network Pharmacology in Yeast for Target Identification 455
16.5	Identification of Protein Targets by Proteomic Analysis on 2D Gels 462
16.6	Validation of Compound Targets by Biochemical Analysis 462
16.7	Next Steps in Drug Development 464
16.8	Concluding Remarks 466 Acknowledgments 467 Abbreviations 467 References 467
17	<b>Marine Natural Products: Biodiscovery, Biodiversity, and Bioproduction</b> 473 <i>Miguel C. Leal and Ricardo Calado</i>
17.1	Introduction 473
17.2	Biodiscovery: What and Where? 474
17.2.1	Taxonomic Trends 475
17.2.2	Geographical Trends 478
17.3	Biodiversity 481
17.3.1	Exploring Marine Biodiversity 481
17.3.2	Protecting Marine Biodiversity 483
17.4	From Biodiscovery to Bioproduction 484
17.5	Concluding Remarks 486 References 487
	<b>Index</b> 491