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 Moteshareie, 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 Assay 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	
0.5.2	Mechanism of Cation Transport 132
6.4	

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 ₂ O ₂ -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	Isoquinoline Alkaloids and Their Analogs: Nucleic Acid and Protein
	Binding Aspects, and Therapeutic Potential for Drug Design 241
	Gopinatha S. Kumar

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
10	The Potential of Peptides and Depsipeptides from Terrestrial and
	Marine Organisms in the Fight against Human Protozoan
	Marine Organisms in the Fight against Human Protozoan Diseases 279
10.1	Diseases 279
	Diseases 279 Jean Fotie Introduction 279
10.1 10.2	Diseases 279 Jean Fotie
	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and
10.2	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281
10.2 10.2.1	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281
10.2 10.2.1 10.2.2	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282
10.2 10.2.1 10.2.2 10.2.3	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285
10.2.1 10.2.1 10.2.2 10.2.3 10.2.4	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7 10.2.8	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7 10.2.8 10.2.9	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290 Hirsutatins and Hirsutellides 291
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7 10.2.8 10.2.9 10.2.10	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290 Hirsutatins and Hirsutellides 291 Alamethicin 292
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7 10.2.8 10.2.9 10.2.10 10.2.11	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290 Hirsutatins and Hirsutellides 291 Alamethicin 292 Gramicidins 293
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7 10.2.8 10.2.9 10.2.10 10.2.11 10.2.12	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290 Hirsutatins and Hirsutellides 291 Alamethicin 292 Gramicidins 293 Kahalalides 294
10.2 10.2.1 10.2.2 10.2.3 10.2.4 10.2.5 10.2.6 10.2.7 10.2.8 10.2.9 10.2.10 10.2.11 10.2.12 10.2.13	Diseases 279 Jean Fotie Introduction 279 Antiprotozoan Peptides and Depsipeptides of Natural Origin and Their Synthetic Analogs 281 Apicidins 281 Almiramides and Dragonamides 282 Balgacyclamides 285 Beauvericins and Allobeauvericin 286 Aerucyclamides 286 Chondramides and Jaspamides 288 Enniatins and Beauvenniatins 289 Gallinamide A, Dolastatin 10 and 15, and Symplostatin 4 290 Hirsutatins and Hirsutellides 291 Alamethicin 292 Gramicidins 293 Kahalalides 294 Lagunamides 295

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	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

11.4	Concluding Remarks 341
	Acknowledgments 342
	Abbreviations 342
	References 342
12	Naturally Occurring Calanolides: Chemistry and Biology 349
	Goutam Brahmachari
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	Selective Estrogen Receptor Modulators (SERMs)
	from Plants 375
	Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan
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	Introduction to the Biosynthesis and Biological Activities
	of Phenylpropanoids 387
	Luzia V. Modolo, Cristiane J. da Silva, Fernanda G. da Silva,
	Leonardo da Silva Neto, and Ângelo de Fátima
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	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

16	From Marine Organism to Potential Drug: Using Innovative Techniques
	to Identify and Characterize Novel Compounds — a Bottom-Up
	Approach 443
	A. Jonathan Singh, Jessica J. Field, Paul H. Atkinson, Peter T. Northcote,
	and John H. Miller
16.1	Introduction 443
16.2	Structural Screening Approach 445
16.2.1	Case Study 1: Colensolide from Osmundaria colensoi 448
16.2.2	Case Study 2: Zampanolide from Cacospongia mycofijiensis 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	Marine Natural Products: Biodiscovery, Biodiversity, and
	Bioproduction 473
	Miguel C. Leal and Ricardo Calado
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

Index 491