Edited by Goutam Brahmachari

Bioactive Natural Products

Chemistry and Biology



Contents

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

1 An Overview 1 Goutam Brahmachari

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
Introduction: Antibiotic Resistance and the Use of Natural Products as a Source for Novel Antimicrobials 9
Chemical Genetics and Genomics 10
Development of GDA Technology 11
The Use of Gene Deletion Arrays (GDAs) to Investigate
MOA 12
Chemical Genetic Interactions 12
Quantifying Genetic and Chemical Genetic Interactions 14
Data Analysis 15
Platforms for Chemical Genomic GDA Studies 17
Why Screen Natural Products in GDAs? 19
Successful Applications of GDA Technology 21
Concluding Remarks 22
Abbreviations 24
References 24

XII Contents

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 <i>37</i>
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 <i>49</i>
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
- 1	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

XIV Contents

Antibacterial Activity of Polyether Antibiotics and Their Derivatives 135
Derivatives 100
Antifungal Activity of Polyether Antibiotics and Their
Derivatives 140
Antiparasitic Activity of Polyether Antibiotics and Their
Derivatives 141
Antiviral Activity of Polyether Antibiotics 144
Anticancer Activity of Polyether Antibiotics and Their
Derivatives 145
Concluding Remarks 153
Abbreviations 154
References 155
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
Introduction 171
Biosynthetic Aspects 172
Synthesis of Flavaglines 174
Chemical Syntheses 174
Biomimetic Synthesis of Flavaglines 179
Synthesis of Silvestrol (6) 182
Pharmacological Properties of Flavaglines 184
Anticancer Activity 184
Anti-inflammatory and Immunosuppressant Activities 190
Cytoprotective Activity 190
Antimalarial Activities 191 Structure Activity Balationships (SABs) 102
Structure – Activity Relationships (SARs) 192
Concluding Remarks 192 Abbreviations 193
References 194
Relefences 174
Beneficial Effect of Naturally Occurring Antioxidants against Oxidative
Stress-Mediated Organ Dysfunctions 199
Pabitra B. Pal, Shatadal Ghosh, and Parames C. Sil
Introduction 199
Oxidative Stress and Antioxidants 200
Mangiferin and Its Beneficial Properties 200
Antioxidant Activity of Mangiferin 200
Anti-inflammatory Activity of Mangiferin 201
Immunomodulatory Effect 202
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_2O_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

XVI Contents

ł	Contents	
•	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
	10	Marine Organisms in the Fight against Human Protozoan
		Diseases 279
		Jean Fotie
	10.1	Introduction 279
	10.1	Antiprotozoan Peptides and Depsipeptides of Natural Origin and
	10.2	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
- 11.1Introduction: 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 Lactones 340

XVIII Contents

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
12.4	Concluding Remarks 369
12.5	Acknowledgment and Disclosure 370
	Abbreviations 370
	References 371
	References 5/1
13	Selective Estrogen Receptor Modulators (SERMs)
13	Selective Estrogen Receptor Modulators (SERMs) from Plants 375
13	from Plants 375
13 13.1	
	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375
13.1 13.2	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376
13.1 13.2 13.3	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377
13.1 13.2	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376
13.1 13.2 13.3	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from
13.1 13.2 13.3 13.4	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381
13.1 13.2 13.3 13.4 13.5	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379
13.1 13.2 13.3 13.4 13.5	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383
13.1 13.2 13.3 13.4 13.5 13.6	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383
13.1 13.2 13.3 13.4 13.5 13.6	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383 Concluding Remarks 383
13.1 13.2 13.3 13.4 13.5 13.6	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383 Concluding Remarks 383 Abbreviations 384 References 384
13.1 13.2 13.3 13.4 13.5 13.6 13.7	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383 Concluding Remarks 383 Abbreviations 384 References 384 Introduction to the Biosynthesis and Biological Activities of Phenylpropanoids 387
13.1 13.2 13.3 13.4 13.5 13.6 13.7	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383 Concluding Remarks 383 Abbreviations 384 References 384 Introduction to the Biosynthesis and Biological Activities of Phenylpropanoids 387 Luzia V. Modolo, Cristiane J. da Silva, Fernanda G. da Silva,
13.1 13.2 13.3 13.4 13.5 13.6 13.7	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383 Concluding Remarks 383 Abbreviations 384 References 384 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
13.1 13.2 13.3 13.4 13.5 13.6 13.7	from Plants 375 Divya Lakshmanan Mangalath and Chittalakkottu Sadasivan Introduction 375 Structure of Estrogen Receptor 376 Estrogen Receptor Signaling 377 Selective Estrogen Receptor Modulators from Plants 379 Molecular Basis of the Distinct SERM Action 381 SERMs in the Treatment of Estrogen-Mediated Cancers 383 Concluding Remarks 383 Abbreviations 384 References 384 Introduction to the Biosynthesis and Biological Activities of Phenylpropanoids 387 Luzia V. Modolo, Cristiane J. da Silva, Fernanda G. da Silva,

- 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
- 15Neuropeptides: 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

XX Contents

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 <i>4</i> 62
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
171	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 17.5	From Biodiscovery to Bioproduction 484 Concluding Remarks 486 References 487

Index 491