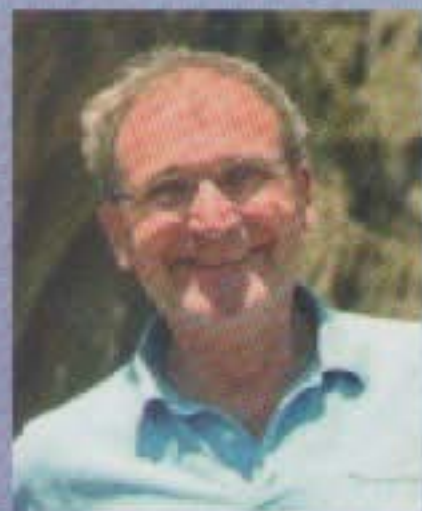
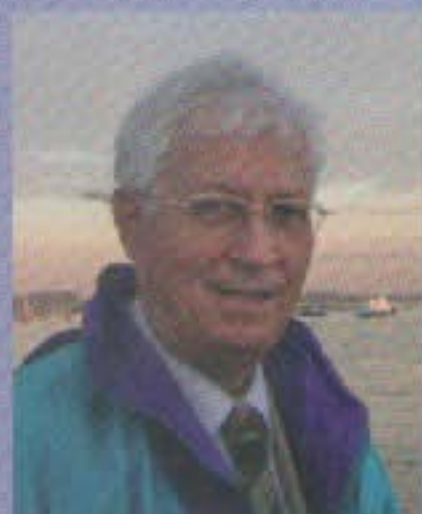
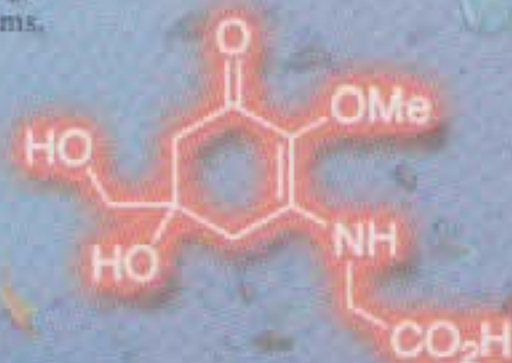


Using a number of outstanding examples, this text introduces readers to the immense variety of marine natural compounds, the methodologies to characterize them, and the approaches to explore their industrial potential. Care is also taken to discuss the function and ecological context of the compounds.

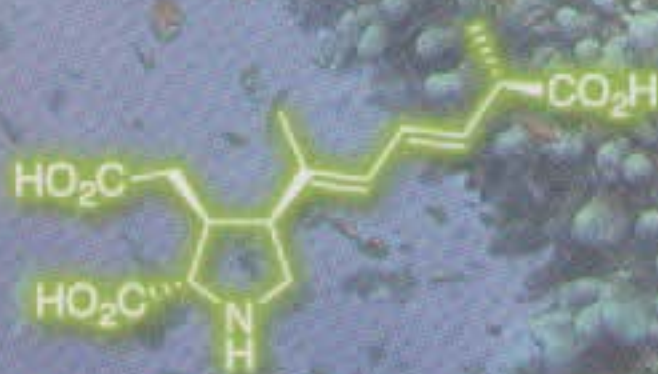
Meticulously produced and easy to read, this book serves students and professionals wishing to familiarize themselves with the field, and is ideally suited as a course book for both industry and academia.



Stéphane La Barre is a senior research scientist at the Centre National de la Recherche Scientifique in France. He gained his MSc from Auckland University, New Zealand, and his PhD from James Cook University, Townsville, Australia, before joining CNRS in 1984. His multi-disciplinary career includes marine chemical ecology, natural products-chemistry of terrestrial and marine organisms, and polymer chemistry. Dr. La Barre is currently the coordinator of the research cluster BioChiMar (Marine Biodiversity and Chemodiversity), and is investigating novel analytical tools to evaluate and predict environmental change affecting coral reef diversity, both biological and chemical.



Jean-Michel Kornprobst is an emeritus professor at the University of Nantes, France, since 2003. Jean-Michel Kornprobst has a chemical engineering degree from Montpellier University and a PhD from the University of Lyon. After being assistant professor at the University of Paris 7 from 1970 to 1973, he became professor of organic chemistry at the University of Dakar, Senegal, where he worked on marine natural products before joining the University of Nantes in 1990. Professor Kornprobst has over 100 publications and three books to his name, and was responsible for two research programs on mangroves in Doha, Qatar, and Jeddah, Saudi Arabia. He has recently been an invited professor at the universities of Louvain-la-Neuve, Belgium, Campinas, Brazil, and Blida, Algeria, and is currently an external member on the scientific advisory board of the Marine Biotechnology Research Center in Québec, Canada.



WILEY Blackwell

ISSN 978-3-527-33465-0



9 783527 334650

Contents

List of Contributors XIII
 Foreword XIX
 Preface XXI

From One Outstanding Marine Molecules from a Chemical
 Annual View 7

101 Marine Cyanotoxins Potentially Harmful to Human Health 3
 Miloune Roué, Muriel Gugger, Stjepko Golubic, Zouher Amzil, Ramulo Araújo, Jean Turquet, Mireille Chinain, and Dominique Laurent
 102 Introduction 3
 103 Marine Cyanobacteria as Causative Agent of Ciguatera-Like Poisoning 4
 104 Ciguatera Fish Poisoning 4
 105 Ciguatera Shellfish Poisoning (CSP): A New Ecotoxicological Phenomenon 7
 106 Ciguatera-Like Poisonings Involve Complex Mixtures of Cyanotoxins 7
 107 Ciguatoxins and Homoanatoxin 7
 108 Ciguatoxins and Saxitoxins 8
 109 Ciguatoxins and Palytoxins 8
 110 Marine Cyanobacteria: A Potential Risk for Swimmers 10
 111 Microcystins Could also be Found in the Sea 12
 112 Risk of Neurodegenerative Disease in the Sea 13
 113 Conclusion and Future Prospects 13
 114 Acknowledgments 16
 115 References 16

116 Outstanding Marine Biotoxins: STX, TTX, and CTX 23
 Philippe Amade, Mohamed Mehiri, and Richard J. Lewis
 117 Introduction 23
 118 Saxitoxins (STXs) in Paralytic Shellfish Poisoning 24
 119 Causes of Paralytic Shellfish Poisoning 24
 120 Saxitoxins (STXs) 24
 121 Chemical Aspects of the STXs 25
 122 Detection of PSP Toxins 27
 123 Poisoning Records 27

2.3 Tetrodotoxin (TTX) in Puffer Fish Poisoning (PFP) 28
 2.3.1 Puffer Fish Poisoning (PFP) 28
 2.3.1.1 Chemical Aspects of TTX 30
 2.3.1.2 Detection of TTXs 32
 2.4 Ciguatoxin (CTX) in Ciguatera Fish Poisoning (CFP) 33
 2.4.1 Ciguatera Fish Poisoning (CFP) 33
 2.4.2 Ciguatoxins 34
 2.4.2.1 Chemical Aspects 35
 2.4.2.2 Detection of CTX Toxins 36
 2.4.2.3 Poisoning Records 37
 2.4.2.4 Persistence and Recurrence of Symptoms 37
 2.4.2.5 Fish Containing Ciguatoxins 37
 2.4.2.6 Qualitative and Quantitative Methods for Toxins Detection 38
 2.5 Conclusions 39
 References 40

3 Impact of Marine-Derived *Penicillium* Species in the Discovery of New Potential Antitumor Drugs 45
 Marieke Vansteelandt, Catherine Roullier, Elodie Blanchet, Yann Guitton, Yves-François Pouchus, Nicolas Ruiz, and Olivier Crovel
 3.1 Introduction 45
 3.2 Molecules Isolated from Marine-Derived *Penicillium* Species With Potent Cytotoxic Activity 46
 3.3 Marine-Derived Cytotoxic *Penicillium* 46
 3.3.1 Where Were Marine-Derived *Penicillium* Searched and Isolated? 46
 3.3.2 Which *Penicillium* Species? 46
 3.4 What are these Promising Molecules from Marine *Penicillium*? 57
 3.4.1 Statistics 57
 3.4.2 Focus on Interesting Molecules 59
 3.4.2.1 Cytotoxic Alkaloids: The Example of Communesins 59
 3.4.3 Cytotoxic Alkaloids/Diketopiperazine Compounds: Examples of Fructigenine A and Verticillin Derivatives 68
 3.4.3.1 Fructigenine A (= Rugulosovin B = Puberullin) 68
 3.4.3.2 Verticillin A and Derivatives 68

- 3.4.4 Cytotoxic Sesquiterpenes: Ligerin, a Chlorinated Sesquiterpene 72
- 3.4.4.1 Ligerin is Produced by a New Species of *Penicillium* 72
- 3.4.4.2 Isolation of Ligerin 72
- 3.4.4.3 The Chlorine Atom: The Originality of Ligerin's Chemical Structure 74
- 3.4.4.4 The Many Structural Analogs of Ligerin 74
- 3.4.4.5 Ligerin Semisynthesis 75
- 3.4.4.6 Bioactivities 75
- 3.5 Conclusions 75
- References 76
- 4 Astonishing Fungal Diversity in Deep-Sea Hydrothermal Ecosystems: An Untapped Resource of Biotechnological Potential? 85**
Gaëtan Burgaud, Laurence Meslet-Cladière, Georges Barbier, and Virginia P. Edgcomb
- 4.1 Introduction 85
- 4.2 Deep-Sea Hydrothermal Vents as Life Habitats 85
- 4.2.1 Generation of Marine Hydrothermal Systems: A Story of Interactions 86
- 4.2.2 Different Vent-Fluid Compositions Shaping Different Ecological Niches 86
- 4.2.3 Hydrothermal Lifestyles At the Macro- and Microscopic Scale 87
- 4.3 The Five "W"s of Marine Fungi: Who? What? When? Where? Why? 89
- 4.3.1 Definition and Novel Concept 89
- 4.3.2 Patterns of Distribution 90
- 4.3.3 Ecological Roles 90
- 4.3.4 Origin of Marine Fungi 91
- 4.4 Fungi in Deep-Sea Hydrothermal Vents 91
- 4.4.1 Hydrothermal Vents as Life Oases for Fungi 92
- 4.4.2 Physiological Adaptations 92
- 4.4.3 Biotechnological Potential 93
- 4.5 Conclusions 94
- Acknowledgments 94
- References 94
- 5 Glycolipids from Marine Invertebrates 99**
Gilles Barnathan, Aurélie Couzinet-Mossion, and Gaëtane Wielgosz-Collin
- 5.1 Introduction 99
- 5.2 Glycosphingolipids from Marine Invertebrates: Occurrence, Characterization, and Biological Activity 101
- 5.2.1 α -Glycopyranosylceramides 102
- 5.2.1.1 α -Monoglycosylceramides 102
- 5.2.1.2 α -Diglycosylceramides 102
- 5.2.1.3 α -Triglycosylceramides 109
- 5.2.1.4 α -Tetraglycosylceramides 109
- 5.2.2 β -Glycopyranosylceramides 109
- 5.2.2.1 β -Glycopyranosylceramides with Saturated, Mono-, and Diunsaturated Sphingoid Bases 109
- 5.2.2.2 β -Glycopyranosylceramides with Triunsaturated Sphingoid Bases 125
- 5.2.3 Biological and Pharmacological Properties of GSLs from Marine Invertebrates 127
- 5.2.3.1 Immunostimulating and Antitumor Properties of α -Galactosylceramides 127
- 5.2.3.2 Biological Activity of β -Glycosylceramides 128
- 5.3 Gangliosides 129
- 5.3.1 Occurrence and Structure 129
- 5.3.1.1 Inositolphosphoceramide Gangliosides 130
- 5.3.1.2 Lactosylceramide Gangliosides 131
- 5.3.1.3 Glucosylceramide Gangliosides 136
- 5.3.2 Biological Activity 143
- 5.3.3 Conclusion 145
- 5.4 Atypical Glycolipids 145
- 5.4.1 Occurrence and Structure 146
- 5.4.2 Biological Activity 152
- 5.4.3 Conclusion 155
- 5.5 General Conclusion 155
- List of Abbreviations 155
- References 155
- 6 Pigments of Living Fossil Crinoids 163**
Cécile Debitus and Jean-Michel Kornprobst
- 6.1 The Discovery of Stalked Crinoids 163
- 6.2 Anthraquinonic Pigments of Stalked Crinoids 165
- 6.3 Axial Chirality of Gymnochromes and Hypochromines 165
- 6.4 Towards a Fungal Origin of Gymnochromes? 167
- 6.5 Biological Activities of Gymnochromes 168
- 6.6 Perspectives 168
- References 169
- Part Two Outstanding Marine Molecules from an Ecological Point of View 171**
- 7 Bacterial Communication Systems 173**
Tilmann Harder, Scott A. Rice, Sergey Dobretsov, Torsten Thomas, Alyssa Carré-Mlouka, Staffan Kjelleberg, Peter D. Steinberg, and Diane McDougall
- 7.1 Coordination of Multicellular Behavior in Bacteria 173
- 7.2 The Repertoire of Chemical Signals 174
- 7.3 Molecular Mechanisms of QS 175
- 7.4 The Effective Range of QS-Regulated Processes 175
- 7.5 The Inhibition of QS: Quorum Quenching 176
- 7.6 Examples of Cross-Kingdom Signaling in the Marine Environment 179
- 7.6.1 Chemical Defense of the Red Seaweed *Delisea pulchra* 179
- 7.6.2 The Mutualistic Association of *Vibrio fischeri* with the Hawaiian Bobtail Squid 180
- 7.6.3 Exploitation of Bacterial QS During Settlement of Marine Spores and Invertebrate Larvae 182

177	"-Omic" Approaches to QS	182	8.7.2	Phosphorus	209
178	Concluding Remarks	183	8.7.3	Nitrogen	209
	References	183	8.7.4	Iron	209
			8.7.5	The Role of Bacteria in the Biosynthesis of DA by Toxicogenic Diatoms	209
18	Domoic Acid	189	8.8	Functional Genomics of Diatoms	210
	<i>Stéphane La Barre, Stephen S. Bates, and Michael A. Quilliam</i>		8.8.1	The Key to the Evolutionary Success of Diatoms	210
181	Historical Background	190	8.8.2	Genomics of DA Biosynthesis and Regulation Networks	210
182	Case Studies	192	8.8.2.1	Genomic Aspects	210
182.1	Case Study #1: The 1987 Outbreak on Prince Edward Island	192	8.8.2.2	Transcriptomics of DA-Producing Diatoms	210
182.2	Case Study #2: The 1991 Bird Intoxication Event in California	193	8.9	Conclusions	210
182.3	Case Study #3: Massive Sea Lion Mortality in Just a Few Weeks	194		Acknowledgments	211
183	Chemistry	194		References	211
183.1	Physico-Chemical Properties	194	9	Algal Morpho-Inducers	217
183.2	Structure Determination	194		<i>Zofia Nehr and Bénédicte Charrier</i>	
183.2.1	The Kainic Acid Family	194	9.1	Introduction	217
183.2.2	Nuclear Magnetic Resonance (NMR) Spectroscopy	195	9.1.1	Marine Macroalgae: Different Evolutionary Histories Leading to Similar Morphologies	217
183.2.3	Mass Spectrometry (MS)	196	9.1.2	Macroalgal Morphologies and Adaptation	217
183.2.4	UV spectroscopy (UV)	196	9.1.3	What Exactly does the Term "Algal Morpho-Inducer" Cover?	219
183.3	Extraction, Separation, Purification, and Detection of DA	197	9.2	Morpho-Inducers of Animals and Land Plants Produced by Macroalgae	219
183.3.1	Extraction and Cleanup	197	9.2.1	Algal Compounds as Morpho-Inducers of Animals	219
183.3.2	Separation and Purification	197	9.2.2	Algal Compounds as Morpho-Inducers of Land Plants: Phytohormones	219
183.3.3	Detection, Quantification, and Monitoring in Food Samples	197	9.2.2.1	Auxins	219
183.3.4	Immunological Method	198	9.2.2.2	Cytokinin	220
183.4	Domoic Acid and Related Molecules	198	9.3	Morpho-Inducers of Macroalgae	220
183.5	Synthesis	198	9.3.1	Are Macroalgal Phytohormones also Morpho-Inducers on Algae?	220
183.6	Biosynthesis	199	9.3.2	Morpho-Inducers of Macroalgae Produced by Bacteria	221
183.6.1	Labeled Precursor Investigations	199	9.4	Conclusions	222
183.6.2	Regulation of DA Production	200		Acknowledgment	222
183.7	Degradation	201		References	222
183.7.1	Photodegradation	201	10	Halogenation and Vanadium Haloperoxidases	225
183.7.2	Photo-oxidative Degradation	201		<i>Jean-Baptiste Fournier and Catherine Leblanc</i>	
183.7.3	Bacterial and Enzymatic Degradation	201	10.1	Introduction	225
184	DA-Producing Organisms	201	10.2	Biochemical Characterization of Vanadium-Dependent Haloperoxidases (VHPOs)	227
184.1	Red Algae	201	10.2.1	Occurrence of VHPO Activities in Living Organisms	227
184.2	Diatoms	202	10.2.2	Enzymatic Assays and Biochemical Properties	228
185	Molecular Basis of DA Acute and Chronic Poisoning	203	10.2.3	Biological Functions of VHPOs	229
185.1	The Kainoids' Mode of Action	203	10.3	Structural Characterization of VHPOs	230
185.1.1	Glutamate Receptors	204	10.3.1	Protein Sequences of VHPOs	230
185.2	Short- and Long-term Neurological Problems Associated with DA	207	10.3.2	Overall Quaternary Structures of VHPOs	231
185.2.1	Mammal Studies	207			
185.3	Cures Against ASP	207			
186	Understanding and Predicting Toxicogenic Diatom Blooms (Macroscopic Scale)	207			
187	Natural Factors that Enhance Bloom Formation and/or DA Production	209			
187.1	Silicon	209			

- 10.3.3 Tertiary Structure of VHPOs 231
- 10.3.4 Active Site Structure of VHPOs 232
- 10.3.5 Fine Structure and Vanadate Coordination into the Active Site 232
- 10.4 Catalytic Cycle and Halide Specificity 234
- 10.4.1 Acid Phosphatases, "Cousins" of VHPOs 234
- 10.4.2 Inhibition of VHPOs 235
- 10.4.3 Reaction with Hydrogen Peroxide 236
- 10.4.4 Oxidation of Halides 236
- 10.4.5 Site-Directed Mutagenesis Studies and Catalytic Mechanisms 236
- References 238
- Part Three Outstanding Marine Molecules with Particular Biological Activities 243**
- 11 Promising Marine Molecules in Pharmacology 245**
Marie-Lise Bourguet-Kondracki and Jean-Michel Komprobst
- 11.1 Introduction 245
- 11.2 Promising Substances Isolated from Microorganisms 248
- 11.2.1 Salinosporamide A 248
- 11.2.2 Thiocoraline 249
- 11.2.3 Ammosamides 251
- 11.2.4 Largazole 252
- 11.3 Promising Substances Isolated from Macroalgae and Invertebrates 254
- 11.3.1 Griffithsin 254
- 11.3.2 PM-050489 and PM-060184; Two New Sponge Polyketides 254
- 11.3.3 Immucothel[®] (Keyhole Limpet Hemocyanin; KLH) 255
- 11.3.4 Jorumycin (Zalypsis[®]) 255
- 11.4 Promising Substances Synthesized from Natural Models 255
- 11.4.1 Plitididepsin from the Ascidian *Aplidium albicans* 255
- 11.4.2 Roscovitine (Seliciclib, CYC202): A Synthetic Analog of Natural Purines 255
- 11.4.3 DMXBA (GTS-21): A Synthetic Analog of Anabaseine 256
- 11.4.4 Bryologs: Synthetic Analogs of Bryostatins 258
- 11.5 Conclusion 259
- References 259
- 12 Promises of the Unprecedented Aminosterol Squalamine 265**
Marie-Lise Bourguet-Kondracki and Jean-Michel Brunel
- 12.1 Introduction 265
- 12.2 Discovery of the Unprecedented Aminosterol Squalamine 265
- 12.3 Syntheses of Squalamine 268
- 12.4 Biological Activities 270
- 12.4.1 Antimicrobial Activities of Squalamine and Its Mimics 270
- 12.4.2 Antiangiogenic Activity of Squalamine 274
- 12.4.3 Antitumor Activity of Squalamine 274
- 12.4.4 Antiviral Activities 275
- 12.5 Mechanism of Antiangiogenic Activity of Squalamine 275
- 12.6 Preclinical Studies of Squalamine 276
- 12.6.1 Antitumor Therapy 276
- 12.6.2 Retinopathy 277
- 12.7 Clinical Studies of Squalamine 277
- 12.7.1 Human Cancers 277
- 12.7.2 Age-Related Macular Degeneration 278
- 12.8 Bioactive Potential of Trodusquemine, a Natural Squalamine Derivative 278
- 12.9 Conclusion 280
- References 280
- 13 Marine Peptide Secondary Metabolites 285**
Bernard Banaigs, Isabelle Bonnard, Anne Witczak, and Nicolas Inguibert
- 13.1 Introduction 285
- 13.2 Ribosomal- and Nonribosomal-Derived Peptides: A Virtually Unlimited Source of New Active Compounds 286
- 13.3 Laxaphycins and their Derivatives: Peptides Not So Easy to Synthesize 291
- 13.4 Dolastatins: From Deception to Hope Through Structural Modification Leading to Reduced Toxicity 294
- 13.5 Didemmins and Related Depsipeptides: How Perseverance Should Lead to Their Low-Cost Production 297
- 13.6 Kahalalide F: A Study in Chemical Ecology as a Starting Point for New Antitumoral Agent Discovery 299
- 13.7 Azole/Azoline-Containing Cyanobactins Isolated from Invertebrates: An Example of Nature's Own Combinatorial Chemistry 304
- 13.8 Conclusion 310
- Acknowledgments 311
- References 311
- 14 Conotoxins and Other Conopeptides 319**
Quentin Kaas and David J. Craik
- 14.1 Background 319
- 14.1.1 Historical Interest in Cone Snails 319
- 14.1.2 Biology of Cone Snails 319
- 14.1.3 Cone Snail Venoms, their Conopeptides and Molecular Targets 320
- 14.2 Diversity of Conopeptides 321
- 14.2.1 Conopeptide Maturation and The Origin of Venom Diversity 321
- 14.2.2 Diversification at the Gene Level 321

14.2.3	Additional Diversity at the Protein Level	322	15.3.1.4	Simple, Effective, and Ubiquitous: Why Change a Winning Recipe?	345
14.2.4	Nomenclature and Classification Schemes	323	15.4	Hermatypic Corals: Living Under Tight Constraints	345
14.2.4.1	Gene Superfamilies	323	15.4.1	Coral Reefs are Monumental Bioconstructions	345
14.2.4.2	Cysteine Frameworks	323	15.4.2	Corals are Highly Efficient Photosynthesizers	345
14.2.4.3	Pharmacological Families	323	15.4.3	High Temperatures and UV Exposures Induce Oxidative Stress and Bleaching in Corals	346
14.3	Isolation Techniques	323	15.4.4	The Chemical Acclimation of Scleractinian Corals to an Exposed Lifestyle	346
14.3.1	Transcriptomics-Based Conopeptide Discovery	324	15.4.5	Biogenic Sources of MAAs in Scleractinian Corals	347
14.3.2	Proteomics Studies of Conopeptides	324	15.4.6	The Phylogenomics of MAAs in Scleractinian Corals	347
14.4	Conopeptide Three-Dimensional Structures	325	15.5	Lichenic Systems: Living in the Extremes	347
14.4.1	Two-Disulfide Conotoxins	325	15.6	Modes of Action and Applications to Human Welfare	348
14.4.2	Tri-Disulfide Conotoxins	327	15.6.1	Skin Care and Cosmetics	349
14.5	Conopeptide Pharmacological Activities	327	15.6.2	Biotechnological Applications	349
14.6	Outlook	328	15.7	Conclusions	349
	Acknowledgments	328		Acknowledgments	349
	References	328	15.A	Appendix 15A.1 Proton NMR data of Mycosporines and Mycosporine-like Amino Acids (MAAs)	350
				Appendix 15A.2 Carbon thirteen data of Mycosporines and Mycosporine-like Amino Acids	354
				References	357
15	Mycosporine-Like Amino Acids (MAAs) in Biological Photosystems	333	16	Extracellular Hemoglobins from Annelids, and their Potential Use in Biotechnology	361
	<i>Stéphane La Barre, Catherine Roullier, and Joël Boustie</i>			<i>Franck Zal and Morgane Rousselot</i>	
15.1	Background	333	16.1	Introduction	361
15.1.1	Life in Full Light and its Constraints	333	16.2	Annelid Extracellular Hemoglobins	362
15.1.2	MAAs: To Protect and Serve, Occasionally to Defend	334	16.3	Architecture	364
15.2	Chemistry	335	16.4	Model of Quaternary Structures	366
15.2.1	Physico-Chemical Characteristics of MAAs	335	16.4.1	Electron Microscopy	366
15.2.2	MAAs and Related Molecules	335	16.4.2	Estimation of Heme Number and Minimal Molecular Weight	367
15.2.2.1	MAAs in the Marine World	335	16.4.3	Small-Angle Light Scattering	368
15.2.2.2	MAAs and Related Molecules in Lichens	335	16.4.4	Low- and High-Pressure Liquid Chromatography and SDS-PAGE	369
15.2.3	Extraction, Separation, Purification, and Detection	335	16.4.5	Electrospray Ionization-Mass Spectrometry	369
15.2.3.1	Extraction, Separation, and Purification	335	16.5	Biotechnology Applications	370
15.2.3.2	Detection, Quantification, and Monitoring in Live Samples	339	16.6	Organ Preservation	370
15.2.4	Structure Determination	339	16.6.1	Preservation Solutions	370
15.2.4.1	Ultraviolet (UV) Spectroscopy	339	16.6.2	Hypothermic Continuous Reperfusion	371
15.2.4.2	Mass Spectrometry (MS)	339	16.7	Anemia	371
15.2.4.3	Nuclear Magnetic Resonance (NMR) Spectroscopy	340	16.7.1	Hemoglobin Oxygen Carriers	372
15.2.5	Synthesis	341	16.7.2	Normovolemic Hemodilution	372
15.2.6	Biosynthesis: Labeled Precursor Investigations	341	16.7.2.1	HEMOXYCarrier [®]	372
15.2.6.1	The Shikimic Acid Pathway	341	16.8	Conclusion	372
15.2.6.2	The Pentose Phosphate Pathway	342		Acknowledgments	373
15.2.7	Regulation of MAA Production: Light and Nutrients	342		References	373
15.2.7.1	Light	342			
15.2.7.2	Nutrients	343			
15.2.8	Degradation	344			
15.3	MAA-Producing Organisms	344			
15.3.1	Chemical Protection Against Abiotic Stress	344			
15.3.1.1	Symbiont-Assisted Metabolism	344			
15.3.1.2	The "ménage à trois" Solution	344			
15.3.1.3	The Chemical Answer to an Exposed Mode of Life	345			

17	Lamellarins: A Tribe of Bioactive Marine Natural Products 377 <i>Christian Bailly</i>	18.7	CPMAS NMR: Obtaining all NMR Observable Nuclei Spectra 425
17.1	Introduction 377	18.8	Conclusion 426
17.2	Lamellarins: Bioactive Marine Natural Products 378		References 428
17.3	Anticancer Activities of Lamellarins 379	19	An Introduction to Omics 431 <i>Jonas Collén and Catherine Boyen</i>
17.4	Inhibition of Topoisomerase I by Lamellarins 380	19.1	What are "Omics"? 431
17.5	Inhibition of Protein Kinases by Lamellarins 380		References 434
17.6	Lamellarin-induced Mitochondrial Perturbations 380	20	Gene Mining for Environmental Studies and Applications: Examples from Marine Organisms 435 <i>Simon M. Dittami and Thierry Tonon</i>
17.7	Antiviral Activity of Sulfated Lamellarins 382	20.1	Introduction 435
17.8	Synthesis of Lamellarins 382	20.2	Techniques 435
17.9	Non-Natural Lamellarin Analogs 383	20.2.1	Sampling and Extraction: An Overview 435
17.10	Conclusion 384	20.2.2	Properties of Nucleic Acids 436
	References 384	20.2.2.1	Genomic DNA 436
		20.2.2.2	RNA 436
		20.2.2.3	mRNA, rRNA, and rDNA 437
		20.2.3	Recent Technological Advances in Molecular Biology and their Impact on Marine Biology 437
		20.2.3.1	Sequencing Technology 437
		20.2.3.2	Gene Expression Profiling 437
		20.3	Current Applications 439
		20.3.1	Development of Genomic and Transcriptomic Resources for Molecular Analysis of Organisms Under Environmental Threats: Application to Coral Physiology 439
		20.3.1.1	Context 439
		20.3.1.2	Selection of Coral Transcriptomics Studies in Relation to Climate Change 440
		20.3.1.3	Concluding Remarks 443
		20.3.2	Search for Genes Involved in Toxin Production within the Dinoflagellate Haystack 443
		20.3.2.1	Context 443
		20.3.2.2	Genes Involved in the Synthesis of Polyketide Dinotoxins 444
		20.3.2.3	Molecular Bases of Dinoflagellate Saxitoxin Production 445
		20.3.2.4	Influence of Abiotic and Biotic Factors on Dinotoxin Biosynthetic Pathways 446
		20.3.2.5	Concluding Remarks 448
		20.3.3	Molecular Biomonitoring of Marine Environments 448
		20.3.3.1	Hierarchical Taxon-Specific and Function-Specific DNA Probes 448
		20.3.3.2	Quantifying Biomass 449
		20.3.3.3	Short and Mid-Term Monitoring of Marine Bacteria and Microalgae 450
		20.3.3.4	Molecular Biomonitoring of Harmful Algae 450
		20.4	Conclusions and Outlook 452
			References 452
Part Four New Trends in Analytical Methods 387			
18	NMR to Elucidate Structures 389 <i>Gaëlle Simon, Nelly Kervarec, and Stéphane Cérantola</i>		
18.1	Introduction 389		
18.2	NMR to Elucidate Structures 389		
18.3	Sample Preparation 390		
18.4	Conventional "Liquid" Probes: Obtaining 1D and 2D Spectra of all NMR-Observable Nuclei 393		
18.4.1	¹ H Spectra 393		
18.4.1.1	Chemical Shift 394		
18.4.1.2	Multiplicity 394		
18.4.1.3	Integration 396		
18.4.1.4	Special Features of Sample 396		
18.4.2	¹³ C Spectra 400		
18.4.3	2D Spectra 402		
18.4.4	Other Nuclei Spectra 408		
18.4.4.1	Isotopes with No NMR Properties 408		
18.4.4.2	Isotopes ($I = 1/2$) with $\approx 100\%$ Abundance 408		
18.4.4.3	Isotopes ($I = 1/2$) with Low Abundance 411		
18.4.4.4	Isotopes ($I > 1/2$) with Long T_1 -Values 415		
18.4.4.5	Isotopes ($I > 1/2$) with Short T_1 -Values 415		
18.5	Cryoprobes: Obtaining 1D and 2D Spectra Mainly in ¹ H, ¹³ C 417		
18.6	HRMAS NMR: Obtaining ¹ H, ¹³ C, ³¹ P, ¹⁵ N 1D and 2D Spectra 417		
18.6.1	Studies of Bacterial Strains from the Marine Deep 420		
18.6.2	Differentiation Between Two Species 421		
18.6.3	Effect of Exposure to Pollutants on Species Metabolism and Possible Pollutant Bioaccumulation 421		
18.6.4	Application of ¹ H HRMAS NMR to Define Organ Cartography 423		
18.6.5	Identification of Different Cultivable Marine Bacteria 424		
18.6.6	Monitoring Quantitative Seasonal Variations of a Molecule 424		
18.6.7	Understanding the Metabolism of a Species 425		

21	Proteomics and Metabolomics of Marine Organisms: Current Strategies and Knowledge 457 <i>Fanny Gaillard and Philippe Potin</i>		
21.1	Introduction 457		
21.2	General Strategies for Proteomics and Peculiarities of the Marine Environment 458		
21.2.1	Protein Extraction 458		
21.2.2	Prefractionation 460		
21.2.3	Quantification 460		
21.2.3.1	Relative Quantification 460		
21.2.3.2	Absolute Quantification 461		
21.2.4	Direct Cell or Tissue Analysis 461		
21.3	General Strategies for Metabolomics, and Peculiarities of the Marine Environment 461		
21.3.1	Experimental Design and Sample Preparation for Metabolomics 462		
21.3.1.1	Experimental Design 462		
21.3.1.2	Sample Preparation 462		
21.3.2	Analytical Tools for Metabolomics 464		
21.3.2.1	Nuclear Magnetic Resonance (NMR) 464		
21.3.2.2	Mass Spectrometry (MS) 464		
21.3.3	Spectral Signal Processing in NMR and MS Metabolomics 465		
21.3.4	Statistical Analysis 466		
21.3.5	Challenges of Metabolite Identification 466		
21.3.6	Current Applications of Marine Metabolomics 466		
21.3.6.1	Health and Disease of Marine Organisms 466		
21.3.6.2	Biodiversity and Chemometry 467		
21.3.6.3	Signals in the Sea: Metabolomics and Marine Chemical Ecology 467		
21.4	Conclusions 468		
	Acknowledgments 468		
	References 469		
22	Genomics of the Biosynthesis of Natural Products: From Genes to Metabolites 473 <i>Olivier Ploux and Annick Méjean</i>		
22.1	Introduction 473		
22.2	Biosynthesis of PKs, NRPs and RiPPs: Basic Principles 474		
22.2.1	The PKSs Polymerize Acetate Units 474		
22.2.2	The NRPSs: A Biological Solid-Phase Peptide Synthesis 475		
22.2.3	Connecting Biosynthetic Genes to Natural Product Structure 475		
22.2.4	The Diversity of RiPPs 476		
22.3	Connecting Genes and Metabolites: Selected Examples of Aquatic Natural Product Biosynthesis 476		
22.3.1	Curacins 477		
22.3.2	Anatoxin-a and Homonatoxin-a 478		
22.3.3	Microcystins 480		
22.3.4	Cyanobactins 482		
22.4	Conclusions and Perspectives 483		
	Abbreviations 483		
	References 484		
23	High-Throughput Screening of Marine Resources 489 <i>Arnaud Hochard, Luc Reininger, Sandrine Ruchaud, and Stéphane Bach</i>		
23.1	Introduction 489		
23.2	High-Throughput Screening and Drug Development 490		
23.2.1	Screening Assay Development and Validation 490		
23.2.2	Statistical Tools for Quality Assessment of HTS Assays 491		
23.2.3	Choice of Screening Strategy 492		
23.2.4	Data Analysis: From Hits to Leads 492		
23.2.4.1	Hits 492		
23.2.4.2	Leads 493		
23.2.5	From HTS Assay to Market: The Drug Development Process 493		
23.3	Examples of High-Throughput Screening 493		
23.3.1	Chemical Libraries: The Fuel of HTS 493		
23.3.2	Biochemical Assay: The Example of Protein Kinases 494		
23.3.3	Protein-Protein Interactions (PPIs) 494		
23.3.4	Cell-Based Assay: The Example of Bryostatins 495		
23.4	Conclusions and Perspectives 495		
	List of Abbreviations 496		
	Acknowledgments 496		
	References 496		
	Index 499		