

Contents

Chapter 1

Bioactive Peptides — Recent Advances and Trends

Horst Kleinkauf and Hans von Döhren

1. Peptides of Ribosomal Origin	2
1.1 Protein antibiotics	2
1.2 Peptide hormones and neuropeptides	2
1.3 Lantibiotics	4
2. Enzymatically Formed Peptides and Polypeptides	6
2.1 Single enzymes or multienzyme	7
2.2 Size of peptide formed	7
2.3 Structure of multienzymes	8
2.4 The thiotemplate mechanism	8
2.5 Enzymic synthesis of peptides	12
3. Genetics of Peptide Synthetases	14
3.1 Siderophores	14
3.2 Bacillus peptides: Gramicidin S, tyrocidine, bacitracin	16
3.3 Genes involved in β -lactam-biosynthesis	17
3.4 More unified approaches to biosynthetic pathways	18
4. New and Old Sources of Peptides	20
5. Conclusions	23
References	26

Chapter 2

Gramicidin S Synthetase

Joachim Vater

1. Introduction	33
2. Purification of Gramicidin S Synthetase	34
3. Physical and Biochemical Properties of Gramicidin S Synthetase	36
4. Reaction Mechanism of the Biosynthesis of Gramicidin S and Product Patterns of Gramicidin S Synthetase	37
5. Reaction Centers for Substrate Activation	40
6. Inhibitor Studies	43
7. Structural Aspects	46
8. Invesigation of Gramicidin S Negative Mutants	49
9. Prospects	50
References	51

Chapter 3

Formation of *N*-methylated Peptide Bonds in Peptides and Peptidols*Andreas Billich and Rainer Zocher*

1. Introduction	57
2. Occurrence of <i>N</i> -methylated Peptide Bonds	57
3. Biosynthesis of <i>N</i> -methylated Peptides	60
4. The <i>N</i> -methyltransferase Function of Enniatin Synthetase	62
4.1 <i>N</i> -methylation of enzyme-bound amino acids	63
4.2 Kinetic properties of the <i>N</i> -methyltransferase function	64
4.3 Inhibition studies of the <i>N</i> -methyltransferase function	64
4.4 Photoaffinity labeling of enniatin synthetase	68
4.5 Monoclonal antibodies to enniatin synthetase	70
5. The <i>N</i> -methyltransferase Function of other Peptides Synthetases	72
5.1 Beauvericin synthetase	72
5.2 Cyclosporin synthetase	73
5.3 Actinomycin synthetases	75
6. Conclusions	76
References	77

Chapter 4

Peptide Bond Synthesis by Enzyme-Catalyzed Acyl-Transfer

Volker Kasche and Günther Michaelis

1. Introduction	81
2. Mechanism of the Kinetically Controlled Peptide Synthesis	83
3. Maximum Yields in the Kinetically Controlled Peptide Synthesis	85
4. Selecting the Optimal Enzyme	89
5. Yield Controlling Factors in the Synthesis of a Peptide Bond with One Enzyme	94
5.1 Protection of the P _i carboxyl group; stereospecificity	94
5.2 pH value	95
5.3 Temperature	96
5.4 Ionic strength	97
5.5 Solvent composition	97
6. Conclusions	98
References	99

Chapter 5

Genetics of Siderophore Biosynthesis and Transport

Volkmar Braun

1. Structure and Function of Siderophores	103
2. F ³⁺ -Aerobactin Transport System	104

2.1 Biosynthesis of aerobactin	104
2.2 Fe ³⁺ -aerobactin transport	111
3. Enterochelin Biosynthesis and Fe ³⁺ -Enterochelin Transport	113
4. Fe ³⁺ -Dicitrate Transport	115
4.1 Transport	115
4.2 Regulation	117
5. Regulation of Iron Transport Systems	118
5.1 Regulation of gene expression	118
5.2 Regulation of the Fe ³⁺ -siderophore receptor activity	120
6. Antibiotics Containing Siderophore Structures	122
6.1 Naturally occurring sideromycins	122
6.2 Synthetic antibiotics with siderophore structures	123
7. Concluding Remarks	124
Acknowledgements	125
References	125

Chapter 6

Discovery of new β -Lactam and β -Lactam like Antibiotics from Bacteria

Hideo Ono and Setsuo Harada

1. Introduction	131
2. Screening Method and Producing Organisms	134
3. Fermentation	135
4. Isolation Procedure	135
5. Chemical Characterization	140
6. Structure Determination	142
7. Biological Activities of Cephabacin, Formadecin and Lactivicin	147
8. Conclusion	155
References	155

Chapter 7

Glycopeptide Antibiotics of the Vancomycin Group

C. Lancini and B. Cavalleri

1. Introduction	159
2. Producing Organisms	161
3. Chemistry	161
4. Biosynthesis	167
5. Mechanism of Action	169
5.1 Effect on growing cultures	169
5.2 Studies with cell free systems	169
5.3 Action at molecular level	170
6. Relation of Antimicrobial Activity and Mechanism of Action	171
References	172

Chapter 8

Peptide Phytotoxins from Plant Pathogenic Fungi

Jonathan D. Walton

1. Introduction	179
2. Host-Selective Toxins	181
2.1 AM-toxin	181
2.2 Host-specific toxin from <i>Alternaria brassicae</i>	183
2.3 Victorin	184
2.4 HC-toxin	188
2.5 PC-toxin	192
3. Non-Selective Toxins	193
3.1 Tentoxin	194
3.2 Enniatins	196
3.3 Peptidic siderophores	196
References	198

Chapter 9

Chemical Synthesis and Bioactivity of Gramicidin S and Related Peptides

Michinori Waki and Nobuo Izumiya

1. Introduction	205
2. Structures of Gramicidin S and Related Natural Peptides	206
2.1 Gramicidin S and its congeners	206
2.2 Tyrocidines	207
2.3 Gratisin	208
3. Chemical Synthesis of Gramicidin S and Related Peptides	208
3.1 Synthesis of linear precursor peptides	208
3.2 Synthesis of cyclic peptides	209
4. Structure-Activity Relationships of Gramicidin S, Tyrocidines and Gratisin	212
4.1 Gramicidin S	212
4.1.1 Funktion of the amino acid residues at positions 1 and 1'	216
4.1.2 Funktion of the amino acid residues at positions 2 and 2'	217
4.1.3 Funktion of the amino acid residues at positions 1,1' and 3,3'	217
4.1.4 Funktion of the amino acid residues at positions 3 and 3'	217
4.1.5 Funktion of the amino acid residues at positions 4 and 4'	218
4.1.6 Funktion of the amino acid residues at positions 5 and 5'	218
4.1.7 Summary by "sidedness" hypothesis	218
4.2 Tyrocidines	219
4.3 Gratisin	221
5. Conformations of Gramicidin S and Tyrocidines	221
5.1 Optical rotatory dispersion (ORD) and circular dichroism (CD)	222
5.2 Nuclear magnetic resonance (NMR)	223
5.3 Other conformational analyses	224
6. Design of Highly Active Analogs of Gramicidin S	224

7. Active Analogs of Gramicidin S Against Gram-negative Bacteria	228
8. Mechanism of Antimicrobial Action of Gramicidin S	230
8.1 Interactions with model membranes	230
8.2 Interactions with bacterial membranes	230
9. Concluding Remarks	234
References	234

Chapter 10

Cyclosporine: Synthetic Studies, Structure-Activity Relationships, Biosynthesis and Mode of Action

Hans G. Fliri and Roland M. Wegner

1. Introduction	246
2. Cyclosporine	250
2.1 Isolation	250
2.2 Structure determination	250
2.3 Other naturally occurring cyclosporines. Nomenclature	252
3. Total Synthesis	253
3.1 Synthesis of MeBmt	254
3.1.1 The Wenger synthesis	254
3.1.2 The Evans synthesis	256
3.1.3 The Seebach synthesis	258
3.1.4 The syntheses of Rich	258
3.1.5 The Schmidt synthesis	259
3.2 Synthesis of cyclosporine	262
4. Chemical Modification of Cyclosporine	266
5. Structure-Activity Relationships	267
6. Conformation of Cyclosporine in the Crystal, in Aprotic Solvents and in Biological Fluids	270
6.1 Crystal and solution conformation	270
6.2 Cyclosporine conformation in biological fluids	271
6.3 Immunochemical study of the cyclosporine conformation in aqueous medium	271
6.4 Immunological studies of cyclosporine and their interpretation in terms of the conformation of the compound in aqueous media	271
6.5 Calculations using molecular dynamics programs indicate that the crystal structure conformation is in water more stable than any others	273
7. Biosynthesis	274
8. Mechanism of Action of Cyclosporine	276
8.1 Effects on T cells	277
8.2 Effects on B cells	279
8.3 Possible intracellular targets for cyclosporine	280
9. Conclusions and Outlook	280
References	282

Chapter 11

Biosynthesis and Chemical Synthesis of Bleomycin

Tomohisa Takita and Yasuhiko Muraoka

1. Introduction	289
2. Biosynthesis and Semisynthesis of Unnatural Congeners	292
2.1 Biosynthesis	292
2.2 Semisynthesis	294
3. Biosynthesis and Chemical Synthesis of Building Blocks of Bleomycin Molecule	295
3.1 Biosynthesis of unusual amino acids	295
3.2 Chemical synthesis of unusual amino acids	297
3.2.1 Synthesis of pyrimidine-containing amino acid (PBA)	297
3.2.2 Synthesis of <i>erythro</i> - β -hydroxy-L-histidine	298
3.2.3 Synthesis of (2S,3S,4R)-4-amino-3-hydroxy-2-methylpentanoic acid (AHM)	299
3.2.4 Synthesis of 2'-(2-aminoethyl)-2,4'-bithiazole-4-carboxylic acid (ABC)	300
4. Biosynthetic and Chemical Construction of Bleomycin Molecule	300
4.1 Biosynthesis of peptide part of bleomycin: deglycobleomycin	300
4.2 Chemical synthesis of deglycobleomycin	302
4.3 Chemical synthesis of the disaccharide moiety for total synthesis of bleomycin	303
4.4 Total synthesis of bleomycin	304
5. Conclusion	306
References	307

Chapter 12

Small Molecular Protease Inhibitors and Their Biological Effects

Takaaki Aoyagi

1. Introduction	311
2. Protease Inhibitors	312
3. Inhibitors Against Endopeptidases	313
4. Enzymatic Activities of Cellular Membrane	317
5. Inhibitors Against Cell Surface Enzymes	320
5.1 Inhibitors against exopeptidases	320
5.2 Inhibitors against enzymes on cellular membrane	328
6. Enzymatic Changes in Various Pathologic Conditions	330
6.1 Roles of catabolic enzymes in muscular dystrophy	330
6.1.1 Murine muscular dystrophy	330
6.1.2 Duchenne muscular dystrophy	335
6.2 Spontaneously hypertensive rats and aminopeptidases	337
6.3 Immunologic diseases and hydrolytic enzymes	342

7. Modification of Metabolic Homeostasis Caused by Low-Molecular-Weight Enzyme Inhibitors	346
7.1 Enzymatic oscillations caused by bestatin	346
7.2 Influence of angiotensin-converting enzyme inhibitor, foroxymithine	349
7.3 Effects of bestatin on hydrolytic enzymes in progressive muscular dystrophy	352
8. Pharmacologic Applications of Enzyme Inhibitors	356
9. Summary	358
Acknowledgements	359
References	359

Chapter 13

Directed Biosynthesis of Neoviridogriseins

Yasushi Okumura

1. Introduction	365
2. Selective Production of Neoviridogriseins by Directed Biosynthesis	367
2.1 Effect of exogenous amino acid on the production of neoviridogriseins	368
2.2 Specific accumulation of neoviridogrisein II by inhibition of proline hydroxylation reaction	371
2.3 Specific accumulation of neoviridogrisein II by the mutant blocked in <i>trans</i> -4-hydroxy-L-proline formation from L-proline	374
3. Summary	377
References	377

Chapter 14

Biochemical Genetical and Biotechnical Aspects of Antibiotic Production via Immobilised Biocatalysis

Erick J. Vandamme

1. Novel Antibiotic Compounds	379
2. Novel Production Ways for Antibiotics	381
3. Total Enzymatic Synthesis of Antibiotics	381
4. Partial Enzymatic Synthesis of Antibiotics	386
5. Antibiotic Fermentation via Immobilised Viable Cells	390
6. β -Lactam-Antibiotic Bioconversions with Immobilised Biocatalysts	392
6.1 Penicillin bioconversions	392
6.2 Cephalosporin bioconversions	397
7. Chiral Side-Chain Production for β -Lactam Antibiotics Synthesis	402
8. Bioconversion of Novel β -Lactam Antibiotics	403
9. Bioconversion of Other Important Antibiotics	404
10. Perspectives	406
References	407

Chapter 15

Compilation of Peptide Structures — A Biogenetic Approach

Hans von Döhren

Introduction	411
General biosynthetic mechanism	411
Compound data	412
Abbreviations and Symbolism	412
Configuration	412
Bonds	412
Abbreviated nomenclature used	412
Cyclic structures	413
Side chain modifications	413
Chain length	413
Combinations of chains	413
Piperidine-type cyclizations	414
Unusual constituents	414
Compilation	415
Index of table	495
List of abbreviations	502
a) compounds	502
b) sources	507
 List of Contributors	 509
Index	511