

# Contents

|   |     |
|---|-----|
| Contributors .....  | ix  |
| Preface .....   | xi  |
| <br>  |     |
| 1. Discovery of New Macrolides  |     |
| KAZURO SHIOMI AND SATOSHI ÔMURA   |     |
| I. Introduction .....   | 2   |
| II. Macrolides from Actinomycetes.....                                      | 8   |
| III. Macrolides from Bacteria Including Myxobacteria.....                   | 22  |
| IV. Macrolides from Fungi .....   | 27  |
| V. Macrolides from Plants and Lichens .....                                 | 31  |
| VI. Macrolides from Insects .....   | 37  |
| VII. Other Macrolides .....   | 40  |
| VIII. Concluding Remarks .....  | 45  |
| References .....  | 46  |
| <br>  |     |
| 2. Discovery of New Macrolides from Marine Organisms                        |     |
| MASAMI ISHIBASHI  |     |
| I. Introduction .....   | 57  |
| II. Macrocyclic Lactones of Marine Organism Origin.....                     | 58  |
| III. Concluding Remarks .....   | 89  |
| References .....  | 89  |
| <br>  |     |
| 3. Chemical Modification of Macrolides                                      |     |
| TOSHIAKI SUNAZUKA, SADAFUMI OMURA, SHIGEO IWASAKI,<br>AND SATOSHI ÔMURA     |     |
| I. Introduction .....   | 99  |
| II. Fourteen-Membered Macrolides .....                                      | 100 |
| III. Sixteen-Membered Macrolide Antibiotics and the Avermectin Family ..... | 145 |
| IV. Concluding Remarks .....  | 164 |
| References .....  | 165 |

## 4. Total Synthesis of Macrolides

TADASHI NAKATA

|  |     |
|--|-----|
| I. Introduction .....                                | 181 |
| II. Synthetic Strategy for Macrolide Synthesis ..... | 182 |
| III. Total Synthesis of Selected Macrolides .....    | 210 |
| IV. Concluding Remarks .....                         | 271 |
| References .....                                     | 275 |

## 5. Biosynthesis, Regulation, and Genetics of Macrolide Production

HARUO IKEDA AND SATOSHI ÔMURA

|   |     |
|---|-----|
| I. Introduction .....                                   | 286 |
| II. Reaction Mechanism of Polyketide Biosynthesis ..... | 287 |
| III. Polyketide Synthase .....                          | 289 |
| IV. Genes Encoding Modular Polyketide Synthase .....    | 295 |
| V. Sugar Biosynthesis .....                             | 314 |
| VI. Genetic Manipulation of PKS Genes .....             | 319 |
| References .....  | 320 |

## 6. Pharmacokinetics and Metabolism of Macrolides

YOSHIRO KOHNO

|   |     |
|---|-----|
| I. Introduction .....                     | 327 |
| II. Pharmacokinetics and Metabolism ..... | 328 |
| III. Drug Interaction .....               | 350 |
| IV. Concluding Remarks .....              | 354 |
| References .....                          | 354 |

## 7. Antimicrobial Macrolides in Clinical Practice

SALVADOR ALVAREZ-ELCORO AND JOSEPH D. C. YAO

|   |     |
|---|-----|
| I. Introduction .....                               | 363 |
| II. Fourteen- and Fifteen-Membered Macrolides ..... | 364 |
| III. Sixteen-Membered Macrolides .....              | 380 |
| IV. Concluding Remarks .....                        | 382 |
| References .....                                    | 382 |

## 8. Ivermectin in Clinical Practice

OSAMU ZAHA, TETSUO HIRATA, FUKUNORI KINJO, AND ATSUSHI SAITO

|   |     |
|---|-----|
| I. Introduction .....                                       | 403 |
| II. Novel Activity of Ivermectin in Clinical Practice ..... | 405 |
| III. Concluding Remarks .....                               | 414 |
| References .....  | 416 |

## 9. Tacrolimus and Other Immunosuppressive Macrolides in Clinical Practice

TADAIHIRO AMAYA, JUN HIROI, AND IRA D. LAWRENCE

|   |     |
|---|-----|
| I. Introduction .....   | 421 |
| II. Tacrolimus, a Brief Developmental History .....   | 424 |
| III. Novel Activity of Tacrolimus and Other Immunosuppressive Macrolides in Clinical Practice ..... | 425 |
| IV. Concluding Remarks .....  | 442 |
| References .....  | 444 |

## 10. Mode of Action and Resistance Mechanisms of Antimicrobial Macrolides

YOSHINORI NAKAJIMA

|   |     |
|---|-----|
| I. Introduction .....   | 453 |
| II. Mode of Action of Macrolide Antibiotics .....               | 454 |
| III. Mechanisms of Resistance to Antimicrobial Macrolides ..... | 472 |
| IV. Important Developments in Macrolide Antibiotics .....       | 485 |
| V. Concluding Remarks .....                                     | 486 |
| VI. Addendum .....  | 487 |
| References .....  | 488 |

## 11. Mode of Action of Macrolides with Motilin Agonistic Activity—Motilides

NOBUHIRO INATOMI, FUMIHIKO SATO, ZEN ITOH, AND SATOSHI ÔMURA

|  |     |
|--|-----|
| I. Introduction .....                      | 501 |
| II. Mode of Action of Motilin .....        | 504 |
| III. Invention of Motilides .....          | 507 |
| IV. Biological Activity of Motilides ..... | 510 |
| V. Clinical Trials of Motilides .....      | 526 |
| VI. Concluding Remarks .....               | 527 |
| References .....                           | 528 |

## 12. Novel Activity of Erythromycin and Its Derivatives

SHOJI KUDOH, ARATA AZUMA, JYUN TAMAOKI, HAJIME TAKIZAWA, KOH NAKATA, AND HAJIME GOTO

|   |     |
|---|-----|
| I. Erythromycin Treatment in Diffuse Panbronchiolitis .....       | 534 |
| II. Inhibition of Chloride Channel .....                          | 541 |
| III. Effects of Macrolides on Cytokine/Chemokine Expression ..... | 546 |
| IV. Modulation of Bacterial Function .....                        | 553 |
| V. New Challenge for Novel Action .....                           | 557 |
| References .....  | 564 |

## 13. Mode of Action of Avermectin

SATOSHI ÔMURA

|   |     |
|---|-----|
| I. Introduction .....   | 571 |
| II. Target of Avermectin Action.....                          | 571 |
| III. Cloning and Structure of Avermectin Binding Protein..... | 572 |
| IV. Concluding Remarks .....                                  | 575 |
| References .....  | 575 |

## 14. Mode of Action of FK506 and Rapamycin

NOBUHIRO TAKAHASHI

|  |     |
|--|-----|
| I. Introduction .....  | 577 |
| II. Initial Cellular Target for FK506 and Rapamycin; Peptidyl<br>Prolyl <i>cis-trans</i> Isomerases (Rotamases, Immunophilins) ..... | 586 |
| III. Target of FK506–FKBP12 Complex: Calcineurin .....   | 599 |
| IV. Target of Rapamycin–FKBP12 Complex: mTOR/FRAP/RFAT .....   | 604 |
| V. Intervention of Intracellular Signaling Pathways by FK506<br>and Rapamycin .....  | 607 |
| References .....   | 611 |

|            |     |
|------------|-----|
| Index..... | 623 |
|------------|-----|