

MACROLIDE ANTIBIOTICS

CHEMISTRY, BIOLOGY, AND PRACTICE

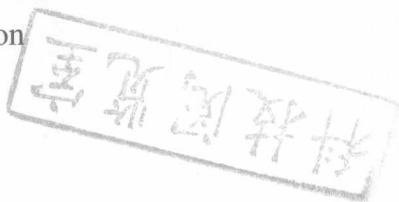
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Edited by
SATOSHI ŌMURA

Macrolide Antibiotics

Chemistry, Biology, and Practice

Second Edition



Edited by

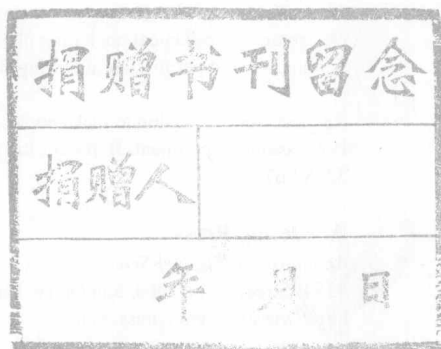
SATOSHI ŌMURA

Kitasato Institute for Life Sciences

Kitasato University

and The Kitasato Institute

Tokyo, Japan



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Macrolide Antibiotics
Chemistry, Biology, and Practice

Contributors

Numbers in parentheses indicate the pages on which the authors' contributions begin.

- SALVADOR ALVAREZ-ELCORO (363), Division of Infectious Diseases, Mayo Clinic, Jacksonville, Florida 32224
- TADAHIRO AMAYA (421), Development Division, Fujisawa Pharmaceutical Company, Osaka, Japan
- ARATA AZUMA (533), Fourth Department of Internal Medicine, Nippon Medical School, Tokyo, Japan
- HAJIMI GOTO (533), School of Medicine, Kyorin University, Tokyo, Japan
- TETSUO HIRATA (403), First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan
- JUN HIROI (421), Medical Science Research, Fujisawa Pharmaceutical Company, Osaka, Japan
- HARUO IKEDA (285), The Kitasato Institute for Life Sciences, Kitasato University, Tokyo, Japan
- NOBUHIRO INATOMI (501), Discovery Research Laboratory III, Takeda Chemical Industries, Ltd., Osaka, Japan
- MASAMI ISHIBASHI (57), Graduate School of Pharmaceutical Sciences, Chiba University, Chiba, Japan
- ZEN ITOH (501), 5-10, Chiyodamachi 1-chome, Maebashi, Gunma, Japan
- SHIGEO IWASAKI (99), The Kitasato Institute, Tokyo, Japan
- FUKUNORI KINJO (403), First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan
- YOSHIRO KOHNO (327), Research Center, Taisho Pharmaceutical Company, Ltd., Saitama, Japan
- SHOJI KUDOH (533), Fourth Department of Internal Medicine, Nippon Medical School, Tokyo, Japan
- IRA D. LAWRENCE (421), Research and Development, Fujisawa Healthcare, Inc., Chicago, Illinois 60015-2548
- YOSHINORI NAKAJIMA (453), Division of Microbiology, Hokkaido College of Pharmacy, Hokkaido, Japan
- KOH NAKATA (533), Research Institute, International Medical Center of Japan, Tokyo, Japan

- TADASHI NAKATA (181), RIKEN, Synthetic Organic Chemistry Laboratory, Saitama, Japan
- SADAFUMI OMURA (99), The Kitasato Institute, Tokyo, Japan
- SATOSHI ÔMURA (1, 99, 285, 501, 571), Kitasato Institute for Life Sciences, Kitasato University, and The Kitasato Institute, Tokyo, Japan
- ATSUSHI SAITO (403), First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan
- FUMIHIKO SATO (501), Pharmacology Laboratory II, Takeda Chemical Industries, Ltd., Osaka, Japan
- KAZURO SHIOMI (1), Kitasato Institute for Life Sciences, Kitasato University, and The Kitasato Institute, Tokyo, Japan
- TOSHIAKI SUNAZUKA (99), School of Pharmaceutical Sciences, Kitasato University, Tokyo, Japan
- NOBUHIRO TAKAHASHI (577), Tokyo University of Agriculture and Technology, Tokyo, Japan
- HAJIME TAKIZAWA (533), Graduate School of Medicine, University of Tokyo, Tokyo, Japan
- JYUN TAMAOKI (533), Tokyo Women's Medical University, Tokyo, Japan
- JOSEPH D. C. YAO (363), Division of Infectious Diseases, Mayo Clinic, Jacksonville, Florida
- OSAMU ZAHA (403), First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan

Preface

Since the first edition of this book was issued in 1984, a number of new macrolides with a variety of characteristics involving not only the structure but also the biological activity have been discovered. Many of these compounds are the results of research achievements on marine natural products that have seen remarkable development during these 18 years. And macrolides having peculiar structures have been chosen as targets for organic syntheses and have contributed greatly to the development of this field.

The analyses of biosynthetic genes on naturally occurring organic compounds is a research field that has recently achieved conspicuous progress. The reader should note in particular that this research has been carried out primarily on the "polyketide," which is the backbone structure of macrolide antibiotics.

Since the first edition was published, semisynthetic macrolide antibiotics such as clarithromycin and roxithromycin and immunosuppressants such as FK-506 (tacrolimus) and rapamycin have been introduced in clinical practice(s) and have shown positive results.

Erythromycin, a representative macrolide, and its derivatives have been found to show excellent anti-diffuse panbronchiolitis activity, and they now receive clinical attention beyond their original use as antibiotics. Moreover, the use of ivermectin, which was initially used as an antinematode agent for animals in 1981, procedures for exterminating onchocerciasis has been undertaken on a large scale. Consequently, in 1999 34 million people in an endemic area centered in Africa were saved from this disease with only a single annual administration. Thus, application of macrolides for clinical use has been a surprising development.

The action mechanism of macrolides with particular activities has been actively investigated. More than ever, macrolides have become interesting compounds in both basic and applied sciences.

In this edition, readers will learn of the development of macrolide research during the past 18 years and its perspective at hand. Each chapter is written by a specialist in that field to explore our fascination with macrolides to its full extent. I am grateful to the author of each chapter.

Finally, I offer hearty thanks to Dr. Shigeo Isawaki and Dr. Noelle Gracy for their valiant efforts and hope that this book will come to the attention of many people and prove useful in their own research fields.

Satoshi Ōmura, Ph.D.
Kitasato University and
The Kitasato Institute
Tokyo, Japan

Contents

Contributors	ix
Preface	xi

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

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

3. Chemical Modification of Macrolides

TOSHIAKI SUNAZUKA, SADAFUMI OMURA, SHIGEO IWASAKI,
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

TADAHIRO 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 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 and Rapamycin	607
References	611
Index	623

Chapter 1

Discovery of New Macrolides

KAZURO SHIOMI
SATOSHI ÔMURA

*Kitasato Institute for Life Sciences, Kitasato University
and The Kitasato Institute
Tokyo, Japan*

I. Introduction.....	2
II. Macrolides from Actinomycetes.....	8
A. Medium-Ring Macrolides (Eight- to Ten-Membered Rings).....	8
B. Twelve-Membered Ring Macrolides	10
C. Fourteen-Membered Ring Macrolides.....	12
D. Sixteen-Membered Ring Macrolides	12
E. Fifteen-, Seventeen-, and Eighteen-Membered Ring Macrolides	13
F. Twenty- to Forty-Eight-Membered Ring Macrolides	14
G. Polyene Macrolides	17
H. Macrodiolides and Macroretrolides	20
I. Macrolide Lactams	21
III. Macrolides from Bacteria Including Myxobacteria	22
A. Eight- to Thirty-Five-Membered Ring Macrolides	22
B. Triene Macrolides.....	25
C. Macrodiolides and Macrotriolides	25
D. Macrolide Lactams and Oxazole-Containing Macrolides.....	26
IV. Macrolides from Fungi	27
A. Eight- to Sixteen-Membered Ring Macrolides	27
B. Cytochalasins	30
C. Macrodiolides, Macrotriolides, and Macropentolides	30
V. Macrolides from Plants and Lichens.....	31
A. Macrolides from Lichens	33
B. Eight- to Nineteen-Membered Ring Macrolides from Plants	33
C. Macrodiolides and Macrotriolides from Plants.....	34
VI. Macrolides from Insects	37
A. Ten- to Thirty-Nine-Membered Ring Macrolides	37
B. Azamacrolides	39
VII. Other Macrolides	40
A. Macrolides from Algae and Invertebrates.....	40
B. Macrolides from Vertebrates	43
VIII. Concluding Remarks.....	45
References	46

I. Introduction

The first edition of this book [1] was published in 1984 and contained information on about 400 macrolides isolated from natural sources. That number has increased to more than 2000. The term *macrolide* was initially proposed by Woodward [2] for macrocyclic lactone antibiotics (e.g., methymycin, pikromycin, and carbomycin), but the term has gradually come to be used in a broader sense [3].

This chapter provides information on macrolides that have been isolated from natural sources and whose structure had been identified by the year 2000. The compounds cited here include macrocyclic lactones having greater than 8-membered rings, regardless of their biosynthetic origins. They consist not only of simple carbocyclic monolactones but also of more complex lactones such as macropolyllides and macrocyclic lactones that contain amino nitrogen, amide nitrogen, an oxazole ring, or a thiazole ring in their skeletons. Ansamacrolides (e.g., rifamycin, maytansine) that have only a lactam ring instead of a lactone are excluded.

Although it would be impossible to collect all natural macrolides reported thus far, more than 2000 compounds have been detected using databases [4–6]. Table I covers most of them. Table I classifies the macrolides according to ring size and compound type, together with the numbers of compounds found for each category. Skeletal structures of these macrolides are characteristically depicted in Fig. 1.

Macrolides with a monolactone ring have a variety of ring sizes up to a 62-membered ring. The ring sizes range from 8- to 42-membered rings, as well as 44-, 48-, and 62-membered rings. Spiroacetal compounds have been isolated as 16-, 22-, 24-, and 26-membered ring macrolides, and many spiroacetal macrolides have biologically important activities. Polyene macrolides contain 16- to 60-membered rings, and their *ene* conjugations are triene, tetraene, pentaene, hexaene, or heptaene. Some cytochalasins have 12- to 15-membered ring lactones. There are macrocyclic lactones having more than one ester linkage, which are called macropolyllides. Macropolyllides include macrodiolides, macrotriolides, macrotetrolides, and macropentolides, each containing di, tri, tetra, and penta ester linkages, respectively, in one macrocyclic ring. Macrocyclic lactones containing nitrogen in their skeletons (azamacrolides and macrolide lactams) and also containing oxazole or thiazole are known to occur in nature.

Macrolide-producing organisms are classified as shown in Table II. Actinomycetes produce the largest number of macrolides (more than 800). Myxobacteria produce about 100 macrolides, and the other bacteria produce about only 40 macrolides. A rather large number of macrolides have been isolated from fungi (about 200). Lichens produce only three compounds. About 70 macrolides have been isolated from algae. Though plants produce about 700 macrocyclic lactone compounds, most of them are tannins or alkaloids such as pyrrolizidines. So they

TABLE I
Numbers of Macrolides Classified by Their Ring Sizes and Structural Characteristics^a

Ring size	Structural characteristic	Number of reported compounds	Ring size	Structural characteristic	Number of reported compounds
Monolactone			36		41
			37		1
8		24	38		5
9		20	39		1
10		55	40		6
10	Nargenicin group	10	41		1
11		2	42		20
12		61	44		2
12	Spinosyn group	23	48		2
13		22	62		2
14		153			
15		7	16	Triene	2
16		243	20	Triene	1
16	Spiroacetal	119	22	Triene	7
17		9	24	Triene	1
18		68	35	Triene	14
19		9	60	Triene	3
20		15			
21		5	26	Tetraene	9
22		19	28	Tetraene	2
22	Spiroacetal	7	38	Tetraene	4
23		3			
24		24	26	Pentaene	1
24	Spiroacetal	11	28	Pentaene	16
25		10	30	Pentaene	3
26		30	32	Pentaene	5
26	Spiroacetal	23	36	Pentaene	3
27		7	44	Pentaene	2
28		3			
29		3	36	Hexaene	2
30		3			
31		9	38	Heptaene	24
32		16			
33		3	12	Cytochalasin	4
34		31	14	Cytochalasin	7
35		1	15	Cytochalasin	1

(continued)

TABLE I (continued)

Ring size	Structural characteristic	Number of reported compounds	Ring size	Structural characteristic	Number of reported compounds
Macropolylide			Other macrolides		
9	Macrodiolide	34	13	Azamacrolide	1
10	Macrodiolide	39	15	Azamacrolide	3
11	Macrodiolide	290	16	Azamacrolide	1
12	Macrodiolide	180			
13	Macrodiolide	21	15	Macrolide lactam	2
14	Macrodiolide	18	17	Macrolide lactam	1
15	Macrodiolide	74	19	Macrolide lactam	3
16	Macrodiolide	73	23	Macrolide lactam	18
18	Macrodiolide	18	24	Macrolide lactam tetraene	1
20	Macrodiolide	1	26	Macrolide lactam	3
22	Macrodiolide	1	28	Macrolide lactam	29
24	Macrodiolide	1	30	Macrolide lactam	2
26	Macrodiolide	1	31	Macrolide lactam triene	12
32	Macrodiolide	9	35	Macrolide lactam	2
40	Macrodiolide	3			
42	Macrodiolide	5	19	Oxazole containing	1
44	Macrodiolide	9	25	Oxazole containing	30
			31	Oxazole containing tetraene	7
12	Macrotriolide	2	37	Oxazole containing	3
14	Macrotriolide	12			
16	Macrotriolide	10	30	Oxazole containing triene macrodiolide	21
18	Macrotriolide	12			
24	Macrotriolide	1			
			19	Thiazole containing macrodiolide	1
15	Macrotetrolide	1			
36	Macrotetrolide	9	Total		2212
24	Macropentolide	6			
25	Macropentolide	1			

^aSkeletal structure of each class compound is characteristically depicted in Fig. 1.

are quite different from polyketide macrolides in their biosynthetic pathways. Macrolides are also obtained from animals. Nearly 200 compounds have been isolated from invertebrates except insects, and most of them have cytotoxicity. Insects produce about 50 compounds, which are very simple macrolides and mainly pheromones. Vertebrates produce about 30 macrolides, most of which have been obtained from the skin surface lipids of horses.

We describe the details of natural macrolides in the following sections classifying according to each producing organism.

Monolactones

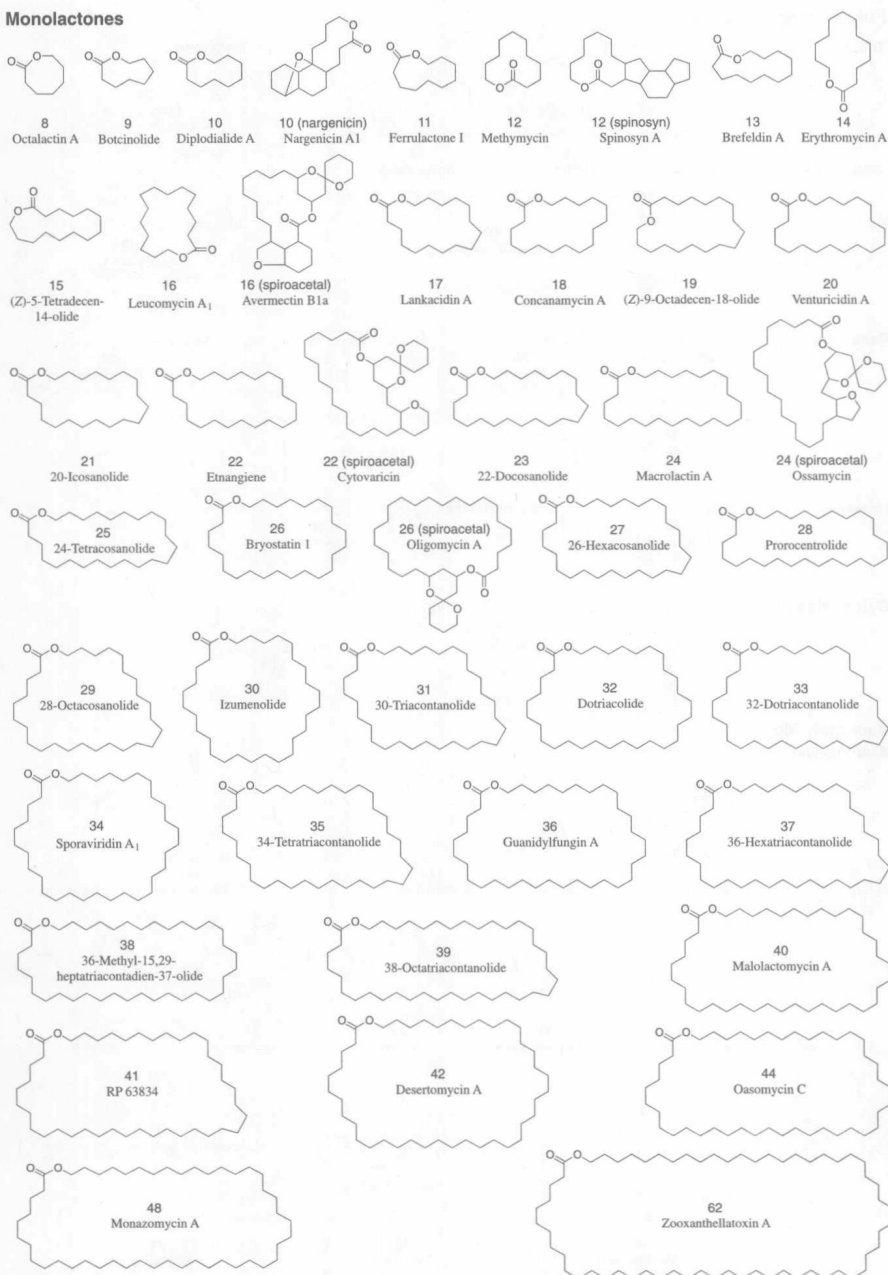
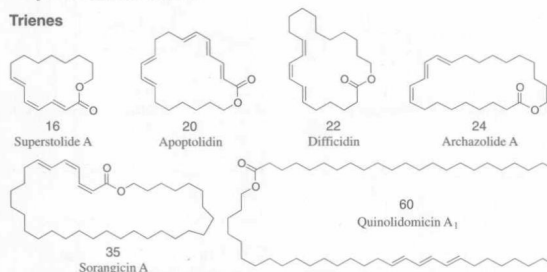


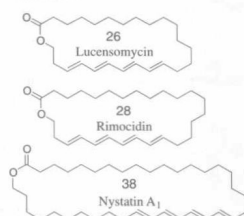
Fig. 1. Skeletons of the macrolides. The compound name for each ring size is the representative compound for each class. These compounds are described in the text.

Polyene monolactones

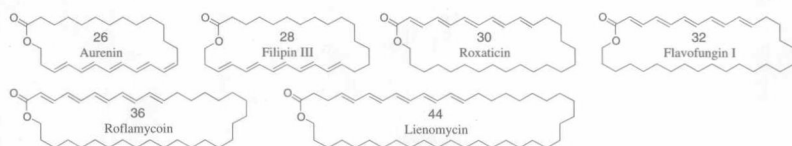
Trienes



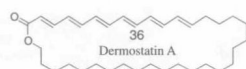
Tetraenes



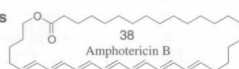
Pentaenes



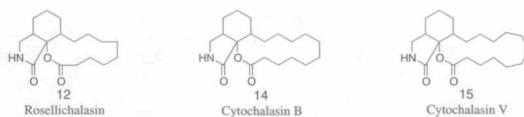
Hexaenes



Heptaenes



Cytochalasins



Macropolyldes

Macrodiolides

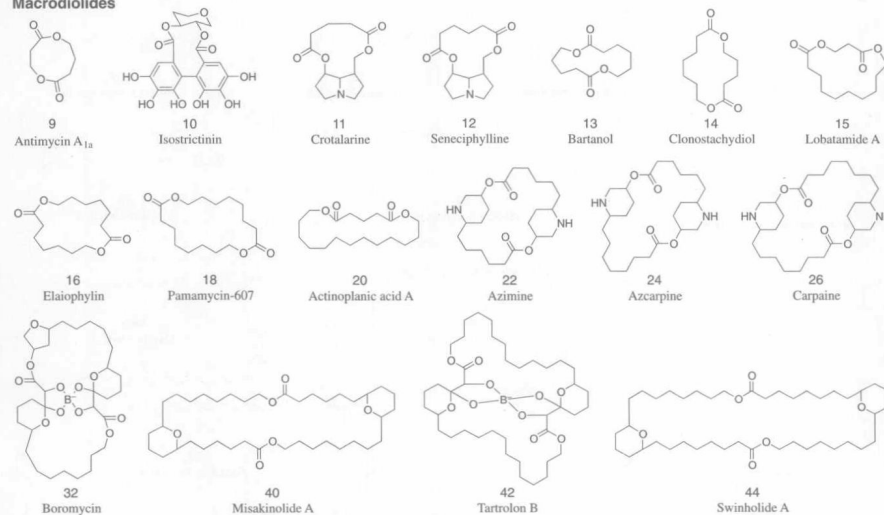


Fig. 1. Continued.