MACROLIDE ANTIBIOTICS

CHEMISTRY, BIOLOGY, AND PRACTICE

SECOND EDITION

Edited by
SATOSHI ŌMURA

Macrolide Antibiotics

Chemistry, Biology, and Practice

Second Edition

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Kitasato Institute for Life Sciences
Kitasato University
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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.

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Chapter 1

Discovery of New Macrolides

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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 macropolylides 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 macropolylides. Macropolylides 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			

[a]Skeletal 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.

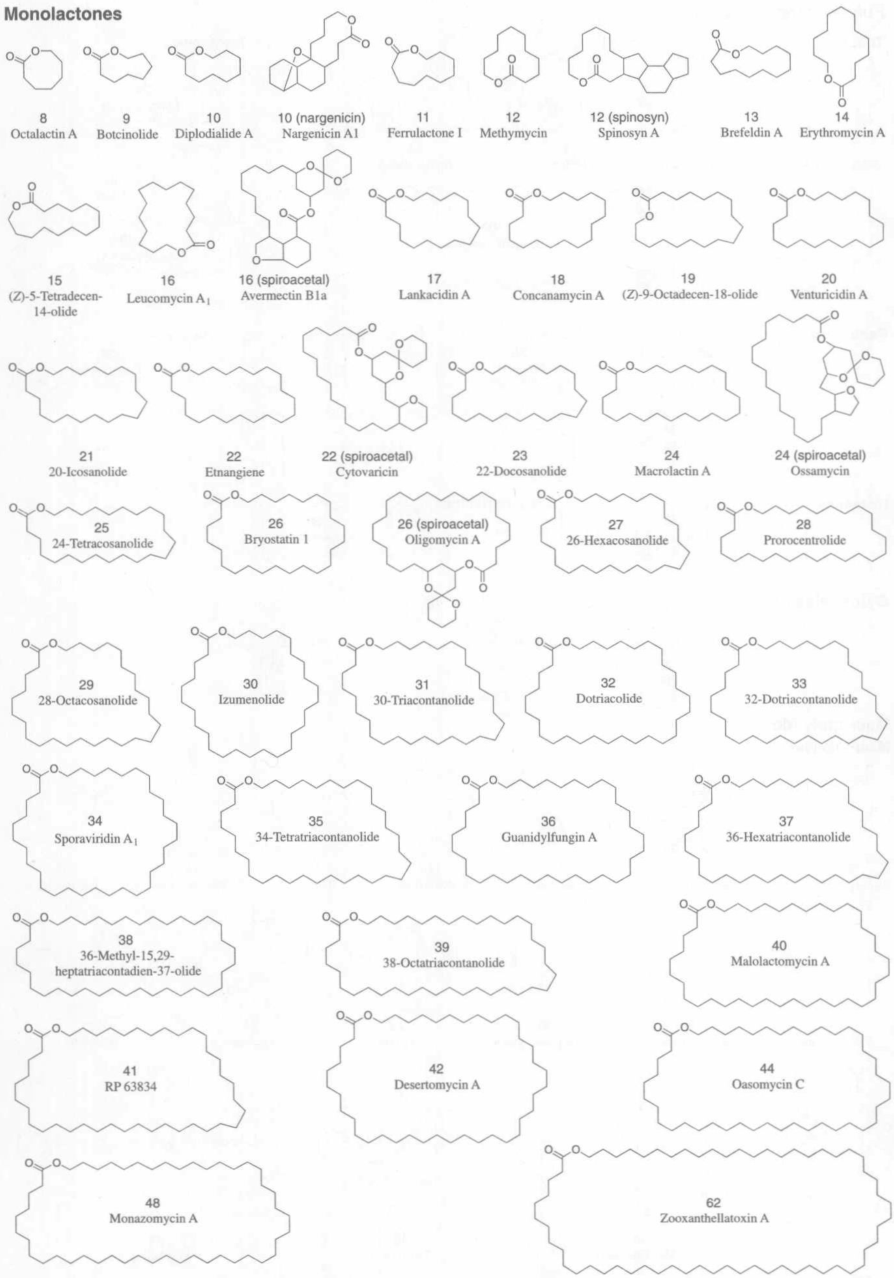

Fig. 1. Skeletons of the macrolides. The compound name for each ring size is the representative compound for each class. These compounds are described in the text.

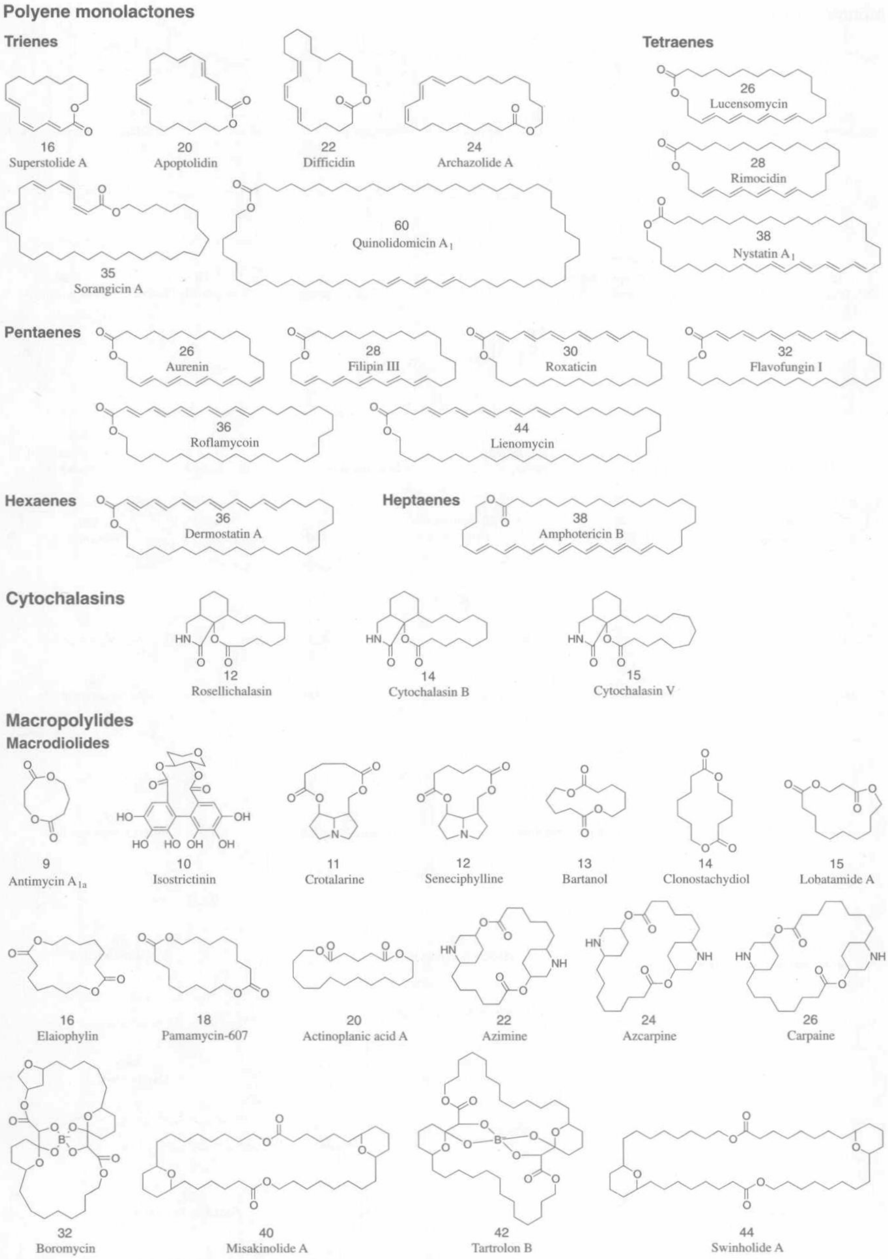

Fig. 1. *Continued.*