ANTIBIOTICS, MACROLIDES

1. Introduction

Macrolide antibiotics are well established antimicrobial agents that are used extensively in both human and veterinary medicine. These agents are orally bioavailable and are generally used to treat infections of the respiratory tract, skin and soft tissues, and genital tract caused by gram-positive microorganisms, *Mycoplasma* species, and certain susceptible gram-negative and anaerobic bacteria.

The macrolide class is large and structurally diverse. The naturally occurring macrolides are produced by fermentation of certain soil microorganisms. The term macrolide was introduced by Woodward (1) to denote that class of substances produced by *Streptomyces* species that contain a macrocyclic lactone. The generalized structure for a macrolide antibiotic is a highly substituted monocyclic lactone (termed an aglycone) with one or more saccharides glycosidically attached to hydroxyl groups on either the aglycone or another saccharide. The various aglycones are formed via polyketide biosynthetic pathways and consequently, they share many similar substituent patterns and stereochemistry, as predicated by those polyketide mechanisms (2,3). The traditional macrolide antibiotics are divided into three families based on the size of the aglycone, which may be a 12-, 14-, or 16-membered ring.

In addition to the many naturally occurring macrolides, many diverse structural modifications have been made over five decades of research using a wide variety of chemical and microbiological methods to produce many semisynthetic derivatives. As a result of these extensive efforts, several of the most important macrolides in current clinical use are semisynthetic compounds. In addition, some promising newer derivatives are undergoing clinical trials and registration activities.

Books devoted solely to macrolides are available (4–6), including a set containing presentations given at the on-going series of Int. Conf. on Macrolides, Azalides, and Streptogramins (ICMAS) conferences (7–10). Journal supplements continue to appear, such as ones for roxithromycin (11), clarithromycin (12), azithromycin (13,14), and dirithromycin (15,16). All aspects of the macrolide field continue to be extensively reviewed; however, only a few recent reviews will be cited that cover the antimicrobial spectrum, pharmacology, and clinical uses of approved agents (17–22) and the research and development of newer derivatives (23–27).

Structures of the older macrolides were comprehensively reviewed in the last volume of *ECT* (28) and thus, not all of them will be repeated here. Many of these complex structures have been targets for synthesis. In 1956, Woodward commented that total synthesis of such complex agents was a hopeless endeavor (29). However, during the intervening years, some macrolides have succumbed to the remarkable advances in both strategy and methodology of synthesis (30–34), and synthesis using the modern technology of combinatorial chemistry even appears to be on the horizon (35,36). The broad variety of structural modifications and formation of numerous semisynthetic derivatives have been extensively reviewed (23–27,37–42).

Most macrolides contain an aminosugar and those compounds are basic substances that form acid addition salts. The amino group is located at either position 3 or 4 of the saccharide. In many macrolides, one or more neutral sugars are present, while a few macrolides possess no aminosugar. The saccharides share some common features: they are usually highly deoxygenated and *N*- and/or *O*-methylated. The most common sugars found in macrolides are given in Table 1.

2. 12-Membered Ring Macrolides

The few macrolides having 12-membered rings are listed in Table 2. Methymycin (**11**, R = OH, R′ = H), isolated from culture broths of a *Streptomyces* species (43), was the first macrolide structure elucidated (44). It is comprised of its aglycone (methynolide) and the aminosugar desosamine (**1**, R = OH, R′ = H) (44,45). Methymycin was the first conventional macrolide to be prepared by total synthesis (46).

Neomethymycin (**11**, R = H, R′ = OH) is an isomer coproduced with methymycin (47). Its aglycone (neomethynolide) was isolated along with methynolide from broths of *S. venezuelae* (48,49). YC-17 (**11**, R = R′ = H), also produced by *S. venezuelae*, is a possible precursor of methymycin and neomethymycin (50). Some of the factors controlling the biosynthesis of methymycin at the polyketide synthase level have recently been elucidated (51,52).

3. Naturally Occurring 14-Membered Macrolides

The most common naturally occurring 14-membered macrolides are given in Table 3.

3.1. Erythromycins. Erythromycin A (**12**, R = OH, R′ = CH_3, R″ = H) is the principal active ingredient in the widely used antibiotic called erythromycin. Erythromycin A is also the main factor found in culture broths of *Saccharopolyspora erythraea* (originally classified as *Streptomyces erythreus*) (53,54). It contains a highly substituted aglycone (erythronolide A: **14**, R = R′ = OH), to which desosamine (**1**, R = OH, R′ = H) and cladinose (**8**, R = CH_3) are attached (55). The complete stereochemistry of erythromycin A was established by X-ray analysis of its hydroiodide dihydrate (56).

Several minor factors are coproduced with erythromycin A. Erythromycin B (**12**, R = R″ = H, R′ = CH_3) lacks a hydroxyl group at C-12 (57). Erythromycin C (**12**, R = OH, R′ = R″ = H) contains mycarose (**8**, R = H) rather than cladinose (**8**, R = CH_3) as the neutral sugar (58). Erythromycin D (**12**, R = R′ = R″ = H) simultaneously lacks the 12-hydroxyl group and contains mycarose (59). Erythromycin F (**12**, R = R″ = OH, R′ = CH_3), which contains a 2-hydroxymethyl group (60,61), may be the biosynthetic precursor of erythromycin E (**13**), which possesses a unique orthoester linkage (62–64). Chemical degradation of erythromycin A yielded its aglycone, erythronolide A (**14**, R = R′ = OH) (65). Biosynthesis of erythromycin A proceeds first through 6-deoxyerythronolide B (**14**, R = R′ = H) and then erythronolide B (**14**, R = H, R′ = OH) (66,67).

The first total synthesis of erythromycin-related compounds was erythronolide B (68); syntheses of erythronolide A and 6-deoxyerythronolide B soon followed (69,70). Completion of the total synthesis of erythromycin A in 1981 is regarded as a landmark achievement (71). Even today, these highly complex structures continue to challenge the insights and skills of organic chemists to assemble them in a concise and elegant manner (30–36).

3.2. Oleandomycin. Oleandomycin (**15**, R = CH_3) was the primary factor in culture broths of *S. antibioticus* (72,73). Its aglycone, oleandolide, differs from the erythronolides at several centers, most notably by the epoxide at C-8. In addition, the neutral sugar in oleandomycin is oleandrose (**10**, R = CH_3) (74–76). A by-product, oleandomycin Y (**15**, R = H), contains the neutral sugar L-olivose (**10**, R = H) (77).

3.3. Pikromycin. Pikromycin (**16**, R = OH, R′ = H), the first macrolide discovered (78,79), is produced by *S. felleus*. Its structure was determined from chemical degradation, mass spectrometry, nuclear magnetic resonance (nmr), and X-ray crystallography (80–85). The key feature of pikromycin and its relatives is the absence of the neutral sugar and the presence of a ketone at C-3. The aglycone, pikronolide, as well as 10,11-dihydropikromycin (**17**, R = OH, R′ = H), have been produced by *S. venezuelae* (48,86). The polyketide synthase in *S. venezuelae* has recently been studied to determine the biosynthetic factors that govern formation of pikromycin versus methymycin in this organism (51,52).

Narbomycin (**16**, R = R′ = H), produced by *S. narbonensis* (87), is 12-deoxypikromycin (88). Its aglycone, narbonolide, is produced by *S. venezuelae* and bioconverted into narbomycin and then pikromycin (89,90). The stereochemistry of narbonolide was established by total synthesis (91). Two derivatives of narbonolide containing mycaminose (**1**, R = R′ = OH) rather than desosamine (**1**, R = OH, R′ = H) were produced by species of *Nocardiopsis*: kayamycin (**17**, R = H, R′ = OH) (92) and the previously known 5-*O*-mycaminosylnarbonolide (**16**, R =, R′ = OH) (93).

3.4. Megalomicins. The megalomicins were the first macrolides obtained from species of *Micromonospora* (*M. megalomicea* and *M. inositola*) (94–96). Structures were determined by nmr and X-ray crystallographic studies (97,98). Megalomicins (**18**) are the only 14-membered macrolides containing two aminosugars: desosamine and a novel aminosugar, megosamine (**3**) glycosidically linked to the 6-hydroxyl group. The megalomicins also differ from erythromycin in that the neutral sugar (cladinose in erythromycin) is either mycarose (**8**, R = H) or its acyl derivative. The aglycones of megalomicin and erythromycin A are identical (95).

3.5. Lankamycins/Kujimycins. The lankamycin/kujimycin group lacks aminosugars but contains the neutral sugars D-chalcose (**7**) and L-arcanose (**6**) or their derivatives. Lankamycin (**19**, R = R′ = $OCCH_3$) was found in culture broths of *S. violaceoniger* (99) and its structure was revised after detailed nmr studies (100,101). Kujimycin A (**19**, R = H, R′ = $OCCH_3$) and kujimycin B (identical to lankamycin) were isolated from broths of *S. spinichromogenes* (102,103).

3.6. Sporeamicins. The sporeamicin group contains a unique bicyclic aglycone that formally involves an intramolecular cyclization in erythromycin between the hydroxyl group at C-12 and the ketone at C-9 followed by oxidation of the C-11 hydroxyl group and 10,11-dehydration (104). Sporeamicin A

(**20**, $R = R' = CH_3$) contains cladinose whereas sporeamicin B (**20**, $R = H$, $R' = CH_3$) contains mycarose as the neutral sugar (105). Sporeamicin C (**20**, $R = CH_3$, $R' = H$) is *N*-demethyl-sporeamicin A (106).

4. Semisynthetic 14-Membered Macrolides

Erythromycin has been the principal subject of modification efforts involving 14-membered macrolides and a substantial history of knowledge and understanding of its chemistry has been acquired since its discovery in the 1950s (23–27,37–42). During the past decade, several semisynthetic derivatives became among the most important macrolide antibiotics in clinical use. New research in the 1990s was focused most significantly on a new series of derivatives termed ketolides, so-called due to their ketone functionality at C-3. At least two ketolides are undergoing clinical trials and new directions continue to be explored to find useful new semisynthetic derivatives.

Decomposition of erythromycin under acidic conditions generates erythromycin 8,9-anhydro-6,9-hemiketal [33396-29-1] (21) and erythromycin 6,9;9,12-spiroketal [23893-13-2] (22); the latter is formed both directly and step-wise from erythromycin (107–110), as shown in Figure 1. The ring-contracted product [105882-69-7] (23) is derived from transacylation in (21) (111,112).

The acid-instability of erythromycin makes it readily susceptible to degradation in the stomach via conversion to these intramolecular cyclization products that lack antimicrobial activity. To mitigate such decomposition, relatively water-insoluble, acid-stable salts, esters, and/or formulations have been developed to protect erythromycin during passage through the stomach, to increase oral bioavailability, and to decrease the inter- and intra-patient variability of oral absorption. These various derivatives and formulations also mask the very bitter taste of macrolides.

Ester derivatives (structure number 24, Table 4) were synthesized soon after the discovery of erythromycin (113–115). They are readily prepared by acylation of the 2′-hydroxyl group; the neighboring 3′-dimethylamino group directs acylation to this site. Commonly used esters of erythromycin are propionate, acetate, ethyl succinate, and ethyl carbonate. 2′-Esters do not bind bacterial ribosomes, and consequently they must hydrolyze back to the parent to exert antibacterial activity (116). Even today, new ester derivatives are still being prepared and evaluated (117). 2′-*O*-Acetylerythromycin stearate, also known as erythromycin acistrate, is one recent ester-salt combination (118), and a new form of erythromycin ethyl succinate (Biolid) has been developed (119).

Ester derivatives of oleandomycin (**15**, $R = CH_3$) were also pursued leading to commercial development of its triacetyl derivative (**25**), known as troleandomycin (TOA), which improved oral bioavailability and taste compared to the parent (120).

Another successful strategy for derivatization of erythromycin employed modification of those functional groups involved in intramolecular cyclizations. The C-9 ketone, C-6 hydroxyl group, C-8 proton, and/or C-11,12-diol of erythromycin were converted into functional groups that participate poorly, if at all, in intramolecular cyclizations. Some derivatives that have been extensively evalu-

ated in preclinical and clinical trials exhibit such desirable properties as better stability under acidic conditions, broader antimicrobial spectrum of activity, greater oral bioavailability, and higher and more prolonged concentrations of antibiotic in serum and tissues.

The 11,12-carbonate of erythromycin (**26**) is an older cyclic carbonate that had greater stability and antibiotic activity by diminishing irreversible formation of intramolecular enol ether (21) (121). A later analogue, the 11-*N*-12-*O*-cyclic carbamate of 11-deoxy-11-(2-dimethylamino)ethylamino-6-*O*-methylerythromycin (A-62514) (122), pioneered a new direction for modification that has been even more significantly extended, as reflected in structures of the new ketolides.

Several structural modifications of the C-9 ketone of erythromycin have been explored; oximes and hydrazones are less prone to intramolecular cyclization, but they often have less antibiotic activity than erythromycin. Synthesis of more complex oxime derivatives resulted in the development of roxithromycin, the 9-[*O*-(2-methoxyethoxy)methyl]oxime (**27**), the first of the newer derivatives of erythromycin to achieve a significant clinical niche (11,123,124). Reduction of the oximes and hydrazones produced 9(*S*)-erythromycylamine (**28**) as the principal product, along with minor amounts of the 9(*R*)-isomer; however, clinical studies showed that both 9(*S*)-erythromycylamine and its *N*-benzylidene derivative were poorly absorbed in humans (125). Evaluation of more complex oxazine derivatives of erythromycylamine led to dirithromycin: [2(*R*)-(2-methoxyethoxy)-ethylidene oxazine (**29**)] (15,16,126,127). A third route to modification of the ketone utilized a Beckmann rearrangement of the 9-oxime to expand the 14-membered ring to a 15-membered intermediate, which was subsequently reduced and *N*-methylated to yield azithromycin (**30**) (13,14,128–131). The term azalide has been applied to these semisynthetic azalactones.

Other approaches to inhibiting intramolecular cyclizations of erythromycin have also proven successful. Clarithromycin (6-*O*-methylerythromycin) (**31**, R = H) was selected for clinical development from a series of O-alkyl derivatives of erythromycin (132,133). Clarithromycin's activity against bacteria such as *Haemophilus influenzae* and its pharmacokinetic profile are significantlyimproved by its 14(*R*)-hydroxy metabolite (**31**, R = OH) (12,134,135). Another approach replaced the C-8 proton of erythromycin with fluorine, which was accomplished by both chemical and bioconversion methods to yield flurithromycin (**32**) (136), which has been subsequently developed as its ethylsuccinate derivative (137).

Although many other derivatives of erythromycin have been prepared and evaluated, they have not been commercially developed and only a very few can be mentioned here. Modifications at C-9 include a series of new oximes (138), 9-*N*-alkyl derivatives of both 9(*S*)- and 9(*R*)-erythromycylamine (139,140), and siderophore conjugates (141). Numerous new azalide derivatives have been prepared, including isomers of azithromycin and 14-membered ring compounds (142–145). New 6-O-unsaturated-alkyl and -aralkyl derivatives have been reported (146). Further modifications of 6-*O*-methyl-11,12-derivatives have yielded both a series of 2,3-anhydro compounds (called anhydrolides) (147,148) and another series of 3-*O*-acyl derivatives (termed acylides) (149). Finally, a novel series of 9,12-epoxy derivatives (**33**) synthesized from enol ether (21)

showed unexpectedly good antibiotic activity (150). These semisynthetic derivatives (oxolides) are structurally similar to the naturally occurring sporeamicins (**20**), whose modifications have also been explored (151).

The most significant development during the 1990s was the discovery and subsequent exploration and development of the ketolides (152–153). The development and spread of microbial resistance to antibiotics became a major concern during the past decade. Thus, the initial disclosure (154) by scientists from Roussel-Uclaf (now Aventis) of a new series of semisynthetic macrolides exhibiting activity against certain macrolide-resistant bacteria provoked a high degree of interest and follow-up research activities. HMR 3004 (**34a**) had initially been selected as the clinical development candidate from this series, but it was subsequently replaced by HMR 3647, now called telithromycin (**34b**) (155–157). Scientists at Abbott Labs have more recently forwarded a second ketolide known as ABT-773 (**34c**) into development (158,159). Judging from the number of recent publications, patents, and presentations, a considerable amount of research into this series is being pursued by several companies and additional new ketolides will likely be made and evaluated for potential clinical advantages (160–164).

5. Naturally Occurring 16-Membered Macrolides

16-Membered macrolides are divided into the leucomycin- and tylosin-related groups, which differ in the substitution pattern of their aglycones. Multifactor complexes are usually produced and some compounds have been isolated from culture broths of different microorganisms and then have been given different names. Most of these 16-membered macrolides were discovered and isolated well before the last decade (28).

The leucomycin complex of 10 factors (type I in Table 5), occasionally called kitasamycin, was produced by *S. kitasatoensis* (165), later reclassified as a species of *Streptoverticillium* (166). After extensive studies, a 16-membered lactone substituted by an aminosugar and a neutral sugar was proposed, with individual factors differing in acylation of the 3- and 4″-hydroxyl groups. X-ray crystallography of demycarosylisoleucomycin A_3 hydrobromide confirmed these structures except in stereochemistry at C-9 (167,168). Interconversion between leucomycin and isoleucomycin had suggested a β configuration for the C-9 hydroxyl group (169,170), but this assignment was later revised to α (171) and then confirmed by X-ray studies (172,173). Josamycin (**35**, R = acetyl, R′ = isovaleryl) was obtained from culture broths of *S. narbonensis* var. *josamyceticus* (174). Although initially reported as a new macrolide, it was later shown to be identical to leucomycin A_3 (175). Josamycin was commercially launched in Japan in 1970 and is now one of the most widely used 16-membered macrolides.

The maridomycin complex of seven factors (**36**) (type II in Table 5), was obtained from culture broths of *S. hygroscopicus* (176–179). The principal difference from the leucomycins is a 12,13-epoxide. Confirmation of structure was obtained from X-ray crystallography and spectroscopy of 9-*O*-acyl derivatives of maridomycin III (178,180).

Carbomycin A (**37**, R = acetyl, R′ = isovaleryl) (Table 5, type III) (also called magnamycin), the first 16-membered macrolide discovered, was isolated from culture broths of *S. halstedii* (181). The 17-membered lactone originally proposed was later revised to a 16-membered lactone (1,182,183). Its absolute stereochemistry was established by correlations with the maridomycins (177,178). Carbomycin is also produced by *S. thermotolerans* (184). The deltamycins, produced by *S. halstedii* subsp. *deltae*, are five related factors that differ in their 4″-*O*-acyl group (185). Deltamycin A_4 is the same as carbomycin A. Deltamycins differ from the leucomycins and maridomycins by having a 12,13-epoxy-9-ketone. Carbomycin B (**38**, R = acetyl, R′ = isovaleryl) (type IV, Table 5), a minor component in the fermentation broths of *S. halstedii*, contains a C-9–C-13 dienone (186).

Many related complexes have been isolated, including the platenomycin complex (initially YL-704) from *S. platensis* subsp. *malvinus* (187,188); a series designated by abbreviations (DHP, DOA) from another strain of *S. platensis* (189); the midecamycin complex (initially SF-837) from *S. mycarofaciens* (190,191); and the espinomycin factors from *S. fungicidicus* var. *espinomyceticus* (192). The turimycin series of 15 components isolated from culture broths of *S. hygroscopicus* are identical to other members of the leucomycin group (193). Niddamycin (**38**, R = H, R′ = butyryl) was isolated from cultures of *S. djakartensis* (194).

The spiramycin complex, also discovered as foromacidine, was isolated from culture broths of *S. ambofaciens* (195–198). Spiramycins I–III, shown in Table 6, are distinguished by a second aminosugar, forosamine (**2**), attached to the 9-hydroxyl group by a β-glycosidic linkage (199). The three primary factors, spiramycin I, II, and III, differ in their 3-*O*-acyl substituent. Two minor factors containing a neutral sugar instead of forosamine, spiramycin U and S, have been found (200). Selective hydrolysis of the terminal sugar yields the respective neospiramycin factors (201); subsequent hydrolysis of forosamine produces the forocidin factors (202).

Aglycones of 16-membered macrolides exist as intramolecularly cyclized hemiketals as a result of the close proximity of the aldehyde and 5-hydroxyl group. Aglycones can differ in their oxidation level at C-9 and C-12,13 (types I–IV, Table 5) and their 3-*O*-substituent. The names often parallel those of the parent macrolides; eg, leuconolide A_1 is the aglycone from any of five leucomycin factors, and platenolide is the aglycone from platenomycin. The Polonovski reaction is generally used to cleave the aminosugar because acid hydrolysis destroys the aglycone before the aminosugar is hydrolyzed (203–205).

The tylosin group of 16-membered macrolides differs from the leucomycins in the substitution pattern of the aglycone. One major difference is the methyl or hydroxymethyl group at C-14; if hydroxymethyl is present, it may have a glycosidic substituent. The most prominent member of this group is tylosin (40, Table 7), an important veterinary antibiotic produced by *S. fradiae* (206). Its structure was deduced by chemical methods (207) and nmr (199). Absolute configuration was established by spectroscopic comparison with leucomycins (208) and later confirmed by correlations based upon X-ray crystallography of biosynthetic precursors (209,210).

Relomycin (Table 7) was found in culture broths of *S. hygroscopicus* and shown to be 20-dihydrotylosin (tylosin D) (211). Macrocin (3‴-*O*-demethyltylosin)

is a minor factor (tylosin C) and the immediate biosynthetic precursor of tylosin that is preferably obtained from a biosynthetically blocked mutant of *S. fradiae* (212–214). 2‴-*O*-Demethylmacrocin (DOMM), obtained from other mutants of *S. fradiae*, is the penultimate precursor of tylosin (213–216). Other mutants of *S. fradiae* yield shunt metabolites of tylosin in which mycinose is altered (215,216). CP-56,064 [88378-53-4] is an analog of tylosin in which mycarose is replaced by amicetose (**5**, R = H, R′ = OH) (217).

Mycarose is selectively hydrolyzed from tylosin under acidic conditions to produce demycarosyltylosin, known as desmycosin (tylosin B). Although analogous hydrolyses have been performed in the leucomycin–spiramycin group, desmycosin exhibits greater antibiotic activity than demycarosyl compounds from the leucomycin group. Hydrolyses of mycarose from macrocin and 3‴-*O*-demethylmacrocin produce lactenocin and 2″-*O*-demethyllactenocin (DOML), respectively. Other mutants of *S. fradiae* that are blocked in oxidation of the C-23 methyl group, attachment of a neutral sugar onto the C-23 hydroxyl group, or oxidation of the C-20 methyl group provide a convenient source of additional tylosin-related macrolides in which mycarose is present and mycinose is absent (213–215). Some of these structures are shown in Table 7.

Other macrolides in this group have a 12,13-epoxide. Angolamycin (**41**, Table 8, S = α-L-mycarosyl), produced by *S. eurythermus* (218) and identical to shincomycin A from *S. flavochromogenes* (219), contains the 2-deoxy aminosugar, angolosamine (**1**, R = H, R′ = OH), but the stereochemistry of its epoxide remains unproven (220,221). Demycarosylangolamycin was isolated from cultures of *Streptomyces* sp. AS-NG-16 and named staphcoccomycin (**41**, S = H) (222). Two aldehyde-reduced analogues were obtained from *Streptomyces* strain 86-070 (223). CP-56,063 [88378-52-3] and its 20-dihydro derivative, CP-56,678, contain amicetose (**5**, R = H, R′ = OH) as the terminal neutral sugar (217). Acumycin (**42**, S = α-L-cinerulosyl) was isolated from culture broths of *S. griseoflavus* (224) and shown by X-ray crystallography to contain cinerulose (**5**, R = O) as the terminal sugar (225). This same compound was isolated from culture broths of *S. fradiae* var. *acinicolor* and designated cirramycin B or B-58941 (226–228). A6888C, produced by *S. flocculus*, contains dihydrocinerulose; its 20-dihydro derivative, A6888X, was also isolated (229). Cirramycin F-1, identical to A6888C, established that the neutral sugar was L-rhodinose (**5**, R = OH, R′ = H) (230). Cirramycin F-2 possesses the 4-epimeric sugar, L-amicetose (**5**, R = H, R′ = OH) (230). M119-a (**42**, S = L-cladinosyl) produced by an alkalophilic actinomycete, differs from the others in the terminal neutral sugar (231).

Many 16-membered macrolides possess a tylosin-type aglycone with only one saccharide, an aminosugar that is either mycaminose or desosamine. These compounds (Table 9) also differ in their degree of oxidation at C-20, C-23, and C-9–C-13 (dienone or epoxyenone). The first macrolide found in this group was cirramycin A_1 (**43**, R = CHO, R′ = OH, R″ = H), obtained from a complex of several factors produced by *S. cirratus* (232). It was later prepared by hydrolysis of cinerulose from cirramycin B (**42**, S = α-L-cinerulosyl) (226). Rosaramicin (formerly rosamicin) was produced by *M. rosaria* and shown to be 4′-deoxycirramycin A_1 (233). Its X-ray crystal structure has been published (234) and the structures of several minor factors have been reported (235,236). Structures of four related compounds from the juvenimicin complex of eight factors,

A_1–A_4 and B_1–B_4, isolated from culture broths of *M. chalcea* var. *izumensis* (237), have been determined. Shortly thereafter, the M-4365 complex of six factors (A_1–A_3 and G_1–G_3), produced by *M. capillata* (238), was reported. From the izenamicin complex of seven factors produced by a *Micromonospora* species, several new products were isolated (239,240). Many compounds isolated from these different mixtures are identical: for example, juvenimicin A_3, M-4365 A_2, and izenamicin A_1 are the same as rosaramicin.

Hydrolysis of both neutral sugars from tylosin yields 5-*O*-mycaminosyltylonolide (OMT) (**44**, R = CHO, R′ = R″ = OH) (207). However, this compound is more conveniently obtained by hydrolysis of mycarose from the fermentation-derived demycinosyltylosin. Analogous hydrolyses of mycarose from DMOT, GS-77-3, and GS-77-1 (Table 7) yield, respectively, 23-deoxy-5-*O*-mycaminosyltylonolide (DOMT), 20-deoxo-5-*O*-mycaminosyl-tylonolide (GS-77-4), and 5-*O*-mycaminosyltylactone (GS-77-2), (Table 9) (213,214,241).

The mycinamicin complex, also found as an AR-5 complex, was isolated from culture broths of *M. griseorubida* (242–244). These compounds, which may have a dienone (**45**) or epoxyenone (**46**) moiety, are listed in Table 10. They contain a 2,3-double bond and a methyl group rather than a two-carbon substituent at C-6 of the aglycone. A hydroxyl group is present at C-14 in mycinamicins II and V. X-ray crystallography established the stereochemistry and absolute configuration of the aglycone as identical to tylosin (40) (244–247). Minor factors were isolated where the C-14 hydroxymethyl group was either unsubstituted or glycosidated (248), and where the aminosugar was lacking (249). In addition to the 10 initial components, 8 other minor factors as well as several biosynthetic precursors have been isolated (250,251). Mycinamicin II (**45**, R = R′ = CH_3, R″ = OH), (miporamicin or mirosamicin) had been investigated in preclinical studies (252), but it has instead been developed as an antibiotic to treat respiratory diseases in poultry (Mylabin) (253).

A few neutral 16-membered macrolides have been isolated. The structure of chalcomycin (**47**, R = CH_3, R′ = OH), produced by *S. bikiniensis*, has been defined by X-ray crystallography (254). It has two neutral sugars, D-chalcose (**7**) and D-mycinose (**9**, R = R′ = CH_3) and an aglycone that resembles the mycinamicins, but differs by a hydroxyl group at C-8 and a methyl group at C-15. The closely related neutramycin (**47**, R = H, R′ = OH), produced by *S. rimosus* (255–257), lacks a substituent at C-6 of the aglycone. These compounds are shown in Table 11. Two 10,11-dihydro analogues of chalcomycin have also been found (258,259). CP-70,662, produced by *S. hirsutus*, may be 8-deoxychalcomycin (260,261).

Also shown in Table 11 is aldgamycin F, produced by *S. lavendulae*, that contains the novel bicyclic sugar, aldgarose (**4**) (262). Its structure (**48**, R = OH) was established by chemical degradation and mass spectrometry (263–265). Aldgamycin E is the 8-deoxy-10,11-dihydro analogue (263–265). Aldgamycin G is 8-deoxyaldgamycin F, obtained from *S. avidinii* (or CP-70,661 from *S. hirsutus*) (260,266). Its *des*-epoxy analogue was isolated from culture broths of *S. anandii* subsp. *swalpus* and named swalpamycin (267).

As with the leucomycin group, several aglycones exist in the tylosin group that differ in the pattern of oxidation and substitution of the lactone. If the aglycone contains an aldehyde, cleavage of the aminosugar yields the hemiketal,

such as tylonolide (**49**, Table 12) (205). The aldehyde-reduced aglycone (**50**) is a biosynthetic intermediate to tylosin (209,213). Four possible mycinolides and corresponding protomycinolides (deoxymycinolides) are exemplified by mycinolide IV (**51**, R = OH) and protomycinolide IV (**51**, R = H) (268).

6. Semisynthetic Derivatives of 16-Membered Macrolides

No significant improvement in activity has yet resulted from single modifications of the 3-, 9-, 2′-, and/or 4″-hydroxyl groups (269,270). 3″-*O*-Acyl derivatives have not been found via fermentation, but chemical acylation of the 3″-hydroxyl group yields products having good antibiotic activity and better pharmacokinetics than the parent macrolides. Two such compounds have been commercially developed: Rokitamycin (52a, 3″-*O*-propionyl-leucomycin A_5) [74014-51-0], $C_{42}H_{69}NO_{15}$, formerly TMS-19-Q (271); and Miokamycin (52b, 9,3″-di-*O*-acetylmidecamycin A_1) [55881-07-7], $C_{45}H_{71}NO_{17}$, also spelled miocamycin (272). The X-ray crystal structure of a rokitamycin hemiketal has recently been published (173). At least part of the *in vivo* improvement arising from 3″-*O*-acylation was attributed to slower elimination of active metabolites from serum (273–275). These compounds are shown in Figure 2.

To extend these trends further, several series of 3″-*O*-methyl-4″-*O*-alkyl and -acyl derivatives of leucomycin-related macrolides have been synthesized; some of these have exhibited improved *in vitro* and *in vivo* antimicrobial activity along with higher and more prolonged concentrations of antibiotic in serum of rodents (276–278). Previously, 3″- and 4″-*O*-substituted derivatives of spiramycin had been synthesized which also showed similar *in vivo* improvements in activity (279,280).

The enhanced activity observed from acylation of the hydroxyl groups of leucomycin prompted analogous studies of tylosin. Bioconversion of tylosin by *S. thermotolerans* yielded 3- and/or 4″-*O*-acyl derivatives possessing increased activity against certain resistant microorganisms and higher concentrations of antibiotic in serum after oral administration (281). From this study, 3-*O*-acetyl-4″-*O*-isovaleryltylosin (AIV-tylosin) [63409-12-1], $C_{53}H_{87}NO_{19}$, (53) was developed as a new veterinary antibiotic. The current two-step manufacturing process involves bioconversion of tylosin in a second fermentation; efforts are underway to genetically engineer the producing organism so that AIV-tylosin can be directly produced in a single fermentation in a more cost-effective manner (282–284).

Some analogous bioconversions of tylosin-related macrolides (285) were extended by cloning and expressing the 4″-*O*-acylase gene in *S. lividans* and bioconverting spiramycin to 4″-*O*-isovalerylspiramycin [129204-11-1], $C_{48}H_{82}N_2O_{15}$, (286,287). Chemical methods for selective 4″-*O*-substitution of tylosin were also developed and one derivative more stable to liver esterases [4″-*O*-(4-methoxyphenylacetyl)tylosin, YM-133] [103360-00-5], $C_{55}H_{85}NO_{19}$, received some preclinical evaluation (288–291). Other studies have explored synthesis and structure–activity relations of 4″-*O*-acyl derivatives of 16-membered macrolides (285, 292–295).

Another successful approach modified the aldehyde moiety of tylosin. Although hydride reduction of the aldehyde reduced activity, other modifications, especially to desmycosin, yielded compounds having good antibiotic potency, better oral bioavailability, and higher and more prolonged concentrations of antibiotic activity in serum (296–299). Similar pharmacokinetic improvements were observed for the structurally related mycinamicins (300). As a result of these advantages, mycinamicin II (miporamicin) (**45**, R = R′ = CH_3, R″ = OH) and 19-deformyl-4′-deoxydesmycosin (TMC-016) [85382-79-2], $C_{38}H_{65}NO_{12}$, received some preclinical study (252,298,301). Reductive amination of the aldehyde in desmycosin yielded another useful series (302–304), from which 20-deoxo-20-(3,5-dimethylpiperidinyl)desmycosin (tilmicosin) [108050-54-0] (54), $C_{46}H_{80}N_2O_{13}$, was selected as a therapeutic agent to control respiratory disease in cattle, pigs, and poultry because of its activity against *Pasteurella* species, oral bioavailability, and prolonged concentrations *in vivo* (305–307).

Derivatives of 5-*O*-mycaminosyltylonolide (**44**, R = CHO, R′ = R″ = OH) have been extensively investigated, but none has yet been commercially successful. Modifications of its 23-hydroxyl group, especially replacements by secondary amino groups, yielded derivatives having excellent activity *in vitro* but lacking good oral efficacy or bioavailability in animals (308,309). Among other derivatives of OMT, metabolism studies of a 23-*O*-benzyl derivative (TMC-101) have been reported (310). More recently, the 3,4′-dideoxy derivative (YM-17K, MC-352 hydrochloride) was briefly investigated (311,312). Newer modifications have been synthesized such as 2-alkyl and 3,4-anhydro derivatives (313,314). Earlier clinical trials of the structurally related macrolide, rosaramicin (**43**, R = CHO, R′ = R″ = H), had been discontinued (315). Recently, CP-163,505 has been synthesized as a new derivative of repromicin arising from an intensive medicinal chemistry program designed to optimize activity against *Pasteurella* species for the treatment of bovine respiratory disease (316–319).

Some additional aldehyde-modified derivatives of tylosin have been reported (320) and the *p*-nitrobenzyl oxime of tylosin (S-5556) was briefly evaluated (321,322). Other modifications of the dienone moiety include 9-amino-tetrahydro derivatives of niddamycin (323) and several epoxy, dihydro, and tetrahydro derivatives of tylosin (324–327). However, it is still uncertain whether any of these semisynthetic 16-membered derivatives will achieve the success of the semisynthetic 14-membered macrolides.

7. Hybrid Macrolides and Combinatorial Biosynthesis

Along with the discovery of ketolides, a second major advance in the 1990s was understanding the genetic basis of macrolide biosynthesis and developing tools and methodology to exploit that knowledge for producing hybrid and structurally novel macrolides. Prior to this, some macrolides had been prepared by synthesis or bioconversion that represented hybrids of structures within the 14-membered family, within the 16-membered family, or between the two families. For example, 3-*O*-cladinosyl derivatives of 16-membered macrolides were synthesized in which cladinose was attached to tylosin derivatives at the 3-hydroxyl group, analogous to the position of this sugar in erythromycin (Table 3) (328). In the

microbiological approach, microorganisms were employed to perform desired chemical transformations (329,330). Bioconversions of aglycones were advanced by use of cerulenin [17397-89-6], $C_{12}H_{17}NO_3$, an inhibitor of fatty acid synthesis, to block biosynthesis of the aglycone normally produced by the bioconverting organism (331). For example, feeding tylactone (protylonolide) (**50**) to the spiramycin-producer, *S. ambofaciens*, yielded four 9-dihydro-9-*O*-forosaminyl derivatives named chimeramycins (332).

The advent of molecular biology opened many new possibilities for producing hybrid macrolides (2,333,334). The initial breakthrough was the recognition of a modular organization for the biosynthetic machinery, called a polyketide synthase (PKS), that was responsible for assembling the macrolide aglycones (335,336). Initial efforts on genetic modifications of the PKS used homologous recombinations in the macrolide-producing organisms. The next significant advance resulted from removing the biosynthetic genes from the producing organism and conducting genetic engineering and heterologous expression in naïve or genetically friendly hosts (337). The field has now advanced to the point where genes can sometimes be deliberately turned on or off or interchanged, or replaced by genes from other sources, with formation of new products often predictably arising as the result of such planned genetic alterations (338–343). This wide-ranging ability to combine, alter, delete, or interchange genes has been termed "combinatorial biosynthesis" (analogous to "combinatorial chemistry") to denote the promise of achieving the biosynthesis of a very large number of new structures representing numerous possible permutations and combinations of structural motifs (344–347). In addition to changes in the PKS-derived aglycones, further changes can be made on post-PKS events such as hydroxylations and glycosidations as well as potential incorporations of non-ribosomal peptidyl moieties (348–351). Although problems still remain to be resolved (352), continued advances in this rapidly developing area of biotechnology, combined with screening for biological activities, clearly heralds a new era for macrolide discovery research.

8. Biological Properties

8.1. Antimicrobial Properties. Macrolides inhibit growth of gram-positive bacteria, *Mycoplasma* species, and certain gram-negative and anaerobic bacteria. Susceptible gram-positive bacteria include many species of staphylococci and streptococci; susceptible gram-negative bacteria include *Bordetella pertussis*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Campylobacter* sp., *Chlamydia* sp., and *Haemophilus ducreyi* (4,17). Although erythromycin has some *in vitro* activity against *Haemophilus influenzae*, it does not exhibit a high level of *in vivo* efficacy. An important susceptible anaerobe is *Propionibacterium acnes*. Many comparative evaluations have been published (4,18–21,353,354), numerous monographs devoted to particular macrolides are available (eg, 11–16), and countless review publications covering all aspects of the field have proliferated during the past decade.

Only a few important highlights regarding antimicrobial activity will be mentioned. Azithromycin (**30**) provided the broadest expansion of the traditional

in vitro macrolide spectrum by its greater activity against gram-negative bacteria, including *H. influenzae* (355). Its *in vitro* activity combined with high tissue concentrations and long *in vivo* half-life allow once-daily dosing for certain clinical indications, and even permit single-dose therapy in some cases of certain sexually transmitted diseases (13,14,130,131,356–359). Roxithromycin, clarithromycin, and dirithromycin are also being used in less frequent and/or shorter dosing schedules for certain therapeutic applications (124,360–362). The human *in vivo* metabolism of clarithromycin to its 14-hydroxy derivative (**31b**) significantly enhanced clinical efficacy, including improved treatment of *H. influenzae* infections (134,361,362). A bacterium, *Helicobacter pylori*, has been implicated as the causative agent of certain gastrointestinal disorders previously considered to have a noninfectious origin, and clarithromycin in particular has been used as one component of a triple therapy regimen that has greatly improved eradication of these infections (363–365). Macrolides continue to play a role in the treatment of *Legionella* infections although newer quinolones are becoming preferred (366,367). Several of the newer macrolides have demonstrated efficacy against a range of non-tuberculous mycobacteria and are components of multidrug cocktails in order to minimize development of microbial resistance (368–371). Efforts are also underway to try to expand the spectrum of potential activity against various other parasitic organisms (372). These examples represent some of the continuing expansion of the antimicrobial spectrum and clinical efficacy of macrolide antibiotics.

Macrolides inhibit growth of bacteria by binding to ribosomes at the 50S peptidyl transferase center and interfering with protein synthesis (373,374). More recently, an additional mechanism was described involving inhibition of 50S ribosomal subunit formation (375). The nature of a macrolide's substituents plays a significant role in determining its detailed mechanism of action (376–378). Although macrolides are generally regarded as bacteriostatic, in some cases they may exert bactericidal activity (379).

Due to overlapping binding sites, bacterial resistance to macrolides is often accompanied by cross-resistance to lincosamide and streptogramin B antibiotics (MLS_B-resistance), which can be either inducible or constitutive (380–382). Traditional 14-membered macrolides generally induce resistance to themselves and to other 14- and 16-membered macrolides, whereas 16-membered macrolides do not generally induce; consequently, one advantage of the latter is their activity against bacteria that are inducibly resistant to erythromycin. However, these 14- and 16-membered macrolides lack activity against constitutively resistant strains (353,354). Bacterial resistance to antibiotics usually results from modification of a target site, enzymatic inactivation, or increased efflux/reduced uptake into bacterial cells. Modification of the macrolide's ribosomal binding site involves methylation of the 23S fraction of ribosomal RNA (380, 382–384). Enzymatic inactivations of macrolides include esterases, phosphorylases, and glycosidases (383,384). A greater role in resistance is being recognized for efflux mechanisms in which drug-transport proteins actively pump antibiotics from the interior of cells (382–386).

A third important development of the 1990s was the heightened concern about the origin and spread of microbial resistance and the potential loss of antibiotics that could effectively treat infections caused by multiple-resistant

microbes. Considerable discussion and debate has occurred about causative or contributing factors, potential changes in medical practices, and long-term solutions (387–393). Thus, the initial report (154) of a new family of macrolides (ketolides) effective against certain macrolide-resistant strains provoked an unusual amount of interest and subsequent research activity. Due to their differences from erythromycin in structure and ribosomal interactions, the ketolides are only weak inducers of resistance and even inhibit some constitutively resistant bacteria (377,378,394–397). As noted earlier, two members of the ketolide family, telithromycin (**34b**) (157,398,399) and ABT-773 (**34c**) (159), have already progressed into clinical development and others are expected to follow.

8.2. Pharmacokinetics and Pharmacology. Older macrolides such as erythromycin exhibit relatively low serum concentrations, short *in vivo* half-lives, highly variable oral absorption, and low oral bioavailability. Diverse improvements in these pharmacokinetic parameters have been accomplished with newer macrolides. Some general quantitative principles and rules have been proposed for optimizing pharmacokinetic properties of drugs (400,401). One major beneficial feature of the newer macrolides is their higher and more prolonged concentrations of antibiotic activity in certain tissues, such as pulmonary sites, that far exceed serum concentrations and thereby enhance efficacy against tissue-associated infections (134,135,402–406). Another benefit of these newer agents is greater intracellular penetration, a necessary condition for activity against intracellular pathogens. Macrolides may even be taken into phagocyctic cells that then concentrate the antibiotic at the site of infection (407). The pharmacokinetic features of macrolides also provide significant postantibiotic effects that may contribute to their efficacy (408,409). In addition, a variety of sub-MIC effects on microbial functions such as virulence and adhesion have been reviewed (410,411). One noteworthy example of sub-MIC effects is the clinical response now well documented for macrolides against panbronchiolitis despite the lack of significant *in vitro* activity against the causative *Pseudomonas* bacterium (412–414).

The complexity of interactions between macrolides and components of the host's immuno-defense system has become more widely recognized even though only partially understood (415–417). Although intensive efforts have been made to uncover general rules for macrolides, the biological effects vary widely for each individual macrolide, biological activity, and test system being studied. However, strong antiinflammatory effects are becoming recognized as another important component that may contribute to the overall effectiveness of macrolides (418–420).

The principal route of macrolide excretion is through the liver. Macrolides may inhibit hepatic metabolic enzymes, particularly cytochrome P-450, and thereby potentially interfere with metabolism of other drugs (421–424). However, dirithromycin and its precursor (erythromycylamine), unlike other macrolides, do not bind to cytochrome P-450 or induce complex formation (421,425). Several macrolides are initially metabolized to products that retain good antibiotic activity, thereby contributing to more persistent efficacious *in vivo* concentrations of antibiotic. Clarithromycin (**31**) is oxidized to its 14(*R*)-hydroxy derivative (134,135). Dirithromycin (**29**) is a pro-drug that converts to erythromycylamine (**28**) *in vivo* (15,127). Miokamycin and rokitamycin (52) undergo deacylations to

other compounds in the leucomycin group (273–275). The importance of metabolism to drug disposition has fostered several models to try to more effectively predict or screen for potential drug interactions (426–428).

The principal side effects of macrolides are gastrointestinal problems, such as pain, indigestion, diarrhea, nausea, and vomiting (429–431). Other side effects are less common (432–434). Molecular interactions between macrolides and phospholipids have been extensively studied, which has led to some correlations between conformational analyses and *in vitro* models (435).

Erythromycin (**12**) and oleandomycin (**15**, R = CH_3) stimulate motility of the gastrointestinal tract in dogs, whereas 16-membered macrolides do not (436,437). This model has been used to select new antibiotic derivatives of erythromycin having reduced potential for causing gastrointestinal upset. Apart from its antimicrobial activity, erythromycin is known to exert a variety of effects on the gastrointestinal tract, including induction of migrating motor complex and increased lower esophageal sphincter pressure and gastric emptying (438–440). At least part of its mechanism of action is proposed to act as an agonist of motilin, an endogenous peptide in the gastrointestinal tract responsible for interdigestive contractility (441–443). SAR studies with *in vitro* and animal contractility models were used to select macrolide derivatives, such as EM-523, EM-574, ABT-229, and GM-611, as prokinetic agents for the potential treatment of gastrointestinal motility disorders (444–447). Further medicinal chemistry studies are being pursued to better understand the molecular mechanisms of action and to design more effective agents (448,449). Other potential directions for pursuing non-antibiotic activities of macrolides include antiinflammatory and immunomodulatory properties (450,451).

9. Biosynthetic Patterns, Conformational Analysis, and Discovery Research

Macrolides are obtained by controlled submerged aerobic fermentations of soil microorganisms. Although species of *Streptomyces* have dominated, species of *Saccharopolyspora*, *Micromonospora*, and *Streptoverticillium* are also well represented among macrolide producers. The ongoing debates over future roles for natural product research programs (452–454) will certainly influence the discovery of additional new macrolides. The potential creation of larger numbers of new structures via biotechnologies such as combinatorial biosynthesis (338–352) parallels the shift to newer, faster, and higher throughput paradigms for antibiotic drug discovery that place greater emphasis on genomics, proteomics, high-volume screening, computational-based strategies, and earlier consideration of potential development problems (400,401,427,455–459).

The biosynthetic steps that convert the PKS-derived aglycone to final product have been traditionally elucidated by bioconversions, blocked mutants, and radiolabeled precursors. More recently, the techniques of modern molecular biology have allowed new approaches via cloning and sequencing of biosynthetic gene clusters, whose identification has been greatly facilitated by their proximity to antibiotic-resistance genes (333). In addition, the importance of regulatory

genes has been recognized and their critical functions are being elucidated (460). The regular pattern of methyl substituents on alternating carbon atoms (propionate or Gerzon's rule) is the result of the placement of methyl groups derived from propionate precursors (1,461). A common pattern found in the stereochemistry of substituents on aglycones (Celmer's model or rules) has been used to predict stereochemistry and identify incorrect assignments (462–465).

Conformational analysis has been used to find and predict conformations that maximize antibiotic activity, using X-ray crystal structures coupled with nmr and circular dichroism (cd) spectra. An early approach utilized the Dale diamond lattice conformational model (466), which was extended to other diamond lattice models (463,467–469). Many studies have used modern nmr analyses coupled with molecular modeling tools to understand and predict macrolide conformations, and more recently, how these structures interact with macromolecular biological targets (435,470–475). Although extensive correlations between conformation and biological activity had not previously been very successful, some recent investigations have helped to explain ribosomal binding of the new ketolides (473,474). Another example is an nmr-based screen that led to a series of novel inhibitors of the erythromycin ribosome methylation (Erm) methyltransferases involved in macrolide resistance (476,477). Future applications of macrolides in biocatalysis and protein engineering have also been suggested (478).

X-ray crystallography and nmr have been applied to study solid-state properties such as polymorphism and solvation in order to find correlations for physicochemical parameters such as stability and solubility with biological features such as absorption and bioavailability (479–481). The chromatographic techniques currently available for the detection and analysis of many natural and semisynthetic macrolides have been comprehensively reviewed (482).

10. Medical and Economic Aspects

Macrolide antibiotics are used clinically to treat infections resulting from susceptible organisms in the upper and lower respiratory tract, skin and soft tissues, and genital tract. They are generally administered orally, although they can be given intravenously. For the latter purpose, a water-soluble salt is used, because macrolides are poorly soluble in water as free bases. Commonly employed acid-addition salts include the lactobionate, gluceptate, tartrate, and phosphate. Macrolides are not administered by intramuscular injection because of severe pain. For oral administration, acid-stable esters, salts, formulations, and coatings are necessary for erythromycin, which is unstable as its unprotected free base under acidic conditions such as those in the stomach. A major renaissance for macrolides occurred after the mid-1980s due to several newer semisynthetic derivatives that exhibited an expanded spectrum of antimicrobial activity coupled with improved pharmacokinetic and pharmacodynamic features. This expansion of macrolide utility and importance is expected to increase once again when the new ketolides reach the market.

Table 13 provides a list of many macrolide products commercially available for use in human medicine (483–485).

Macrolides are regarded as among the safest antibiotics (486). The principal side effects, which in some cases are sufficiently severe to require cessation of the drug, are gastrointestinal.

Relatively few macrolides are used in veterinary medicine (487–489). The most important is tylosin (Tylan, Elanco Products), which is used in several different forms to control respiratory diseases in poultry, pigs, and cattle, and as a growth promotant for pigs and poultry. It was recently approved for use against the newly recognized bacterium, *Lawsonia intracellularis*, to treat porcine proliferative enteropathy (PPE; also called ileitis) in pigs (490). Other older macrolides in veterinary use include erythromycin, oleandomycin, and spiramycin (487). Newer macrolides developed solely for veterinary applications are the previously mentioned 3-*O*-acetyl-4″-*O*-isovaleryltylosin (53) and tilmicosin (54).

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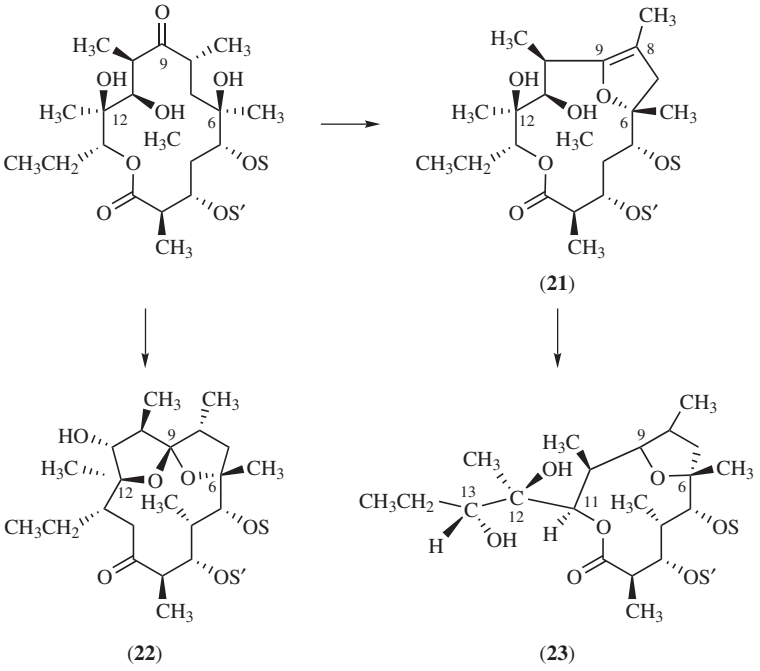
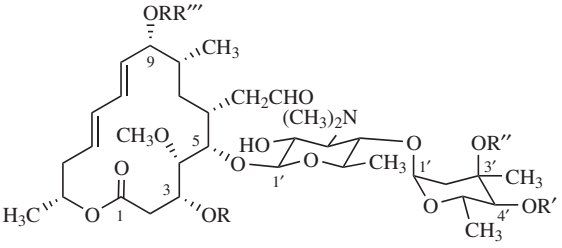
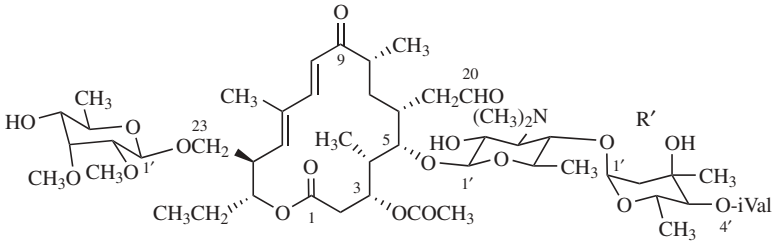


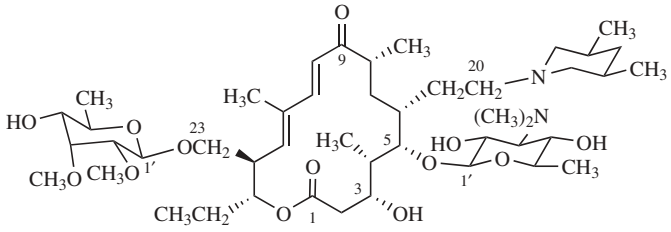
Fig. 1. Intramolecular cyclization reactions of erythromycin A where S = desosamine (**1**, R =OH, R′ =H) and S′ = cladinose (**8**, R =CH_3).



(**52**)



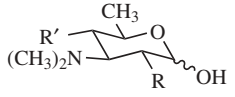
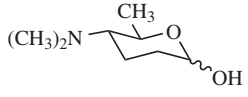
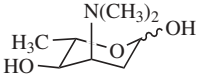
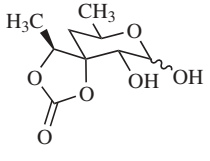
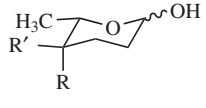
(**53**)



(**54**)

Fig. 2. Semisynthetic derivatives of 16-membered macrolides rokitamycin (52a, R=R‴= H, R′=butyryl, R″=propionyl); miokamycin (52b, R=R′=propionyl, R″=R‴=acetyl); AIV-tylosin (53); and tilmicosin (54).

Table 1. **Saccharides Found in Macrolide Antibiotics**

Saccharide	CAS Registry number	Molecular formula	Structure number	Structure
		Aminosaccharides		
D-angolosamine	[14702-57-9]	$C_8H_{17}NO_3$	1(R = H,R′ = OH)	
D-desosamine	[5779-39-5]	$C_8H_{17}NO_3$	1(R = OH,R′ = H)	
D-mycaminose	[519-21-1]	$C_8H_{17}NO_4$	1(R = R′ = OH)	
D-forosamine	[18423-27-3]	$C_8H_{17}NO_2$	2	
L-megosamine	[65832-97-5]	$C_8H_{17}NO_3$	3	
		Neutral saccharides		
D-aldgarose	[26428-87-5]	$C_9H_{14}O_6$	4	
L-amicetose	[67528-19-2]	$C_6H_{12}O_3$	5(R = H,R′ = OH)	
L-cinerulose	[33985-39-6]	$C_6H_{10}O_3$	5(R + R′ = O)	
L-rhodinose	[35903-48-1]	$C_6H_{12}O_3$	5(R = OH,R′ = H)	

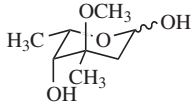
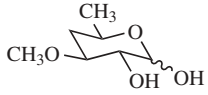
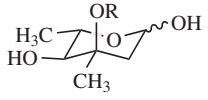
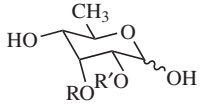
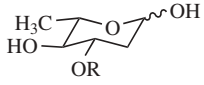
L-arcanose	[26548-40-3]	$C_8H_{16}O_4$	6	
D-chalcose	[3150-28-5]	$C_7H_{14}O_4$	7	
L-cladinose	[470-12-2]	$C_8H_{16}O_4$	8(R = CH_3)	
L-mycarose	[6032-92-4]	$C_7H_{14}O_4$	8(R = H)	
D-6-deoxyallose	[4348-84-9]	$C_6H_{12}O_5$	9(R = R′ = H)	
D-javose	[921-90-4]	$C_7H_{14}O_5$	9(R = H,R′ = CH_3)	
D-mycinose	[21967-31-7]	$C_8H_{16}O_5$	9(R = R′ = CH_3)	
L-oleandrose	[6786-76-1]	$C_7H_{14}O_4$	10(R = CH_3)	
L-olivose	[25029-50-9]	$C_6H_{12}O_4$	10(R = H)	

Table 2. **Macrolides Having a 12-Membered Ring**

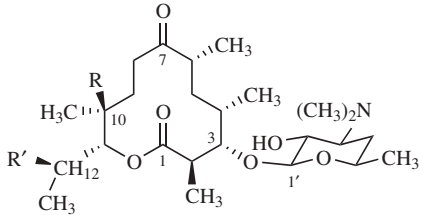
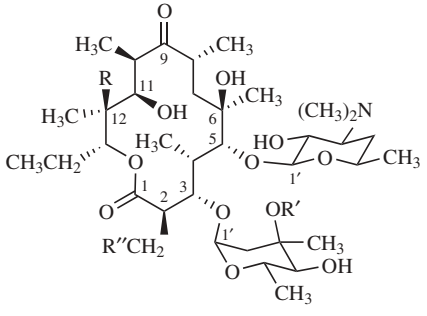
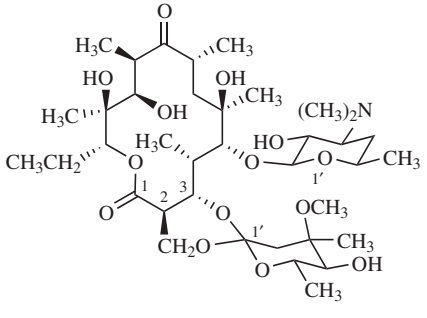
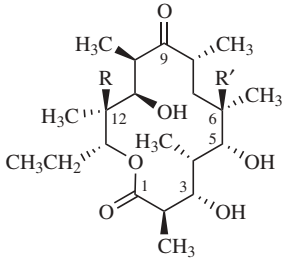
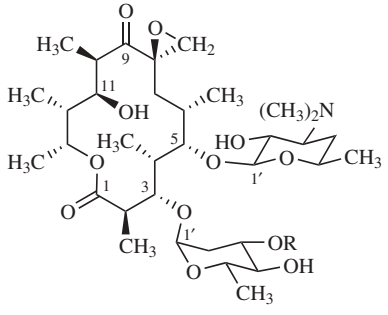
Macrolide	CAS Registry number	Molecular formula	Structure number	Structure
methymycin	[497-72-3]	$C_{25}H_{43}NO_7$	11(R =OH, R′ =H)	
neomethymycin	[497-73-4]	$C_{25}H_{43}NO_7$	11(R =H, R′ =OH)	
YC-17	[11091-33-1]	$C_{25}H_{43}NO_6$	11(R = R′ =H)	

Table 3. **Naturally Occurring 14-Membered Macrolides**

Macrolide	CAS Registry Number	Molecular formula	Structure number	Structure
		Erythromycins and erythronolides		
erythromycin A	[114-07-8]	$C_{37}H_{67}NO_{13}$	12 (R = OH, R′ = CH_3, R″ = H)12 (R = R″ = H, R′ = CH_3)	
erythromycin B	[527-75-3]	$C_{37}H_{67}NO_{12}$		
erythromycin C	[1675-02-1]	$C_{36}H_{65}NO_{13}$		
erythromycin D	[33442-56-7]	$C_{36}H_{65}NO_{12}$		
erythromycin F	[82230-93-1]	$C_{37}H_{67}NO_{14}$	12 (R = OH, R′ = R″ = H)12 (R = R′ = R″ = H)12 (R = R″ = OH, R′ = CH_3)	
erythromycin E	[41451-91-6]	$C_{37}H_{65}NO_{14}$	13	
erythronolide A	[26754-37-0]	$C_{21}H_{38}O_8$	14 (R = R′ = OH)14 (R = H, R′ = OH)14 (R = R′ = H)	
erythronolide B	[3225-82-9]	$C_{21}H_{38}O_7$		
6-deoxyerythronolide B	[15797-36-1]	$C_{21}H_{38}O_6$		

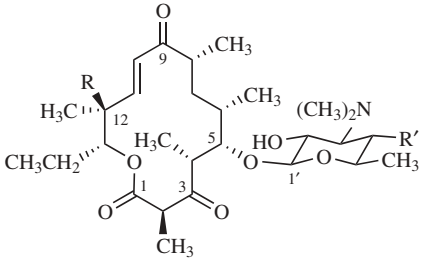
Oleandomycin and related compounds

oleandomycin	[3922-90-5]	$C_{35}H_{61}NO_{12}$	15 (R = CH_3)
oleandomycin Y	[64743-16-4]	$C_{34}H_{59}NO_{12}$	15 (R = H)

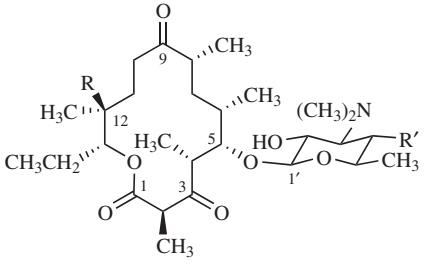


Pikromycin and related compounds

pikromycin	[19721-56-3]	$C_{28}H_{47}NO_8$	16 (R = OH, R′ = H)
narbomycin	[6036-25-5]	$C_{28}H_{47}NO_7$	16 (R = R′ = H)
5-*O*-mycaminosylnarbonolide	[61435-20-9]	$C_{28}H_{47}NO_8$	16 (R = H, R′ = OH)

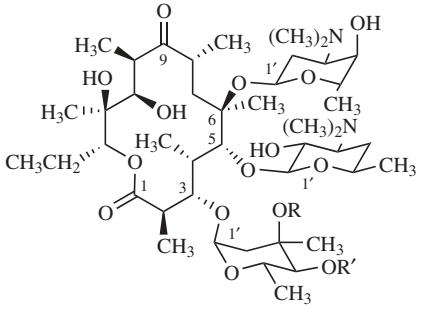


10,11-dihydropikromycin	[27656-56-0]	$C_{28}H_{49}NO_8$	17 (R = OH, R′ = H)
kayamycin[a]	[102907-96-0]	$C_{28}H_{49}NO_8$	17 (R = H, R′ = OH)



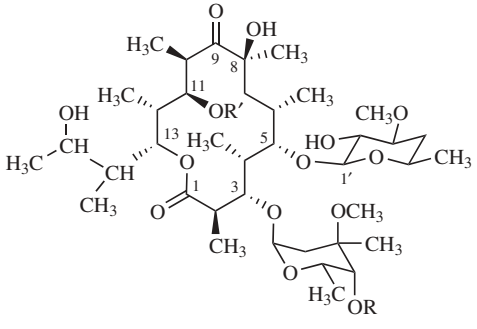
Megalomicins

megalomicin A[b]	[28022-11-9]	$C_{44}H_{80}N_2O_{15}$	18 (R = R′ = H)18 (R = H, R′ = $OCCH_3$)
megalomicin B[c]	[49669-75-2]	$C_{46}H_{82}N_2O_{16}$	
megalomicin C_1[d]	[49669-76-3]	$C_{48}H_{84}N_2O_{17}$	
megalomicin C_2[e]	[49669-77-4]	$C_{49}H_{86}N_2O_{17}$	18 (R = R′ = $OCCH_3$)18 (R = $OCCH_3$, R′ = $OCCH_2CH_3$)18 (R = H, R′ = $OCCH_2CH_3$)
XK-41-B_2	[50692-34-7]	$C_{47}H_{84}N_2O_{16}$	

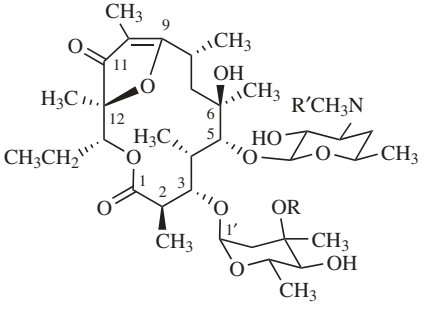


Lankamycin and related compounds

lankamycin (kujimycin B)	[30042-37-6]	$C_{42}H_{72}O_{16}$	19 (R = $OCCH_3$, R′ = OH, R″ = H)19 (R = H, R′ = OH, R″ = H)
kujimycin A	[33955-27-0]	$C_{40}H_{70}O_{15}$	

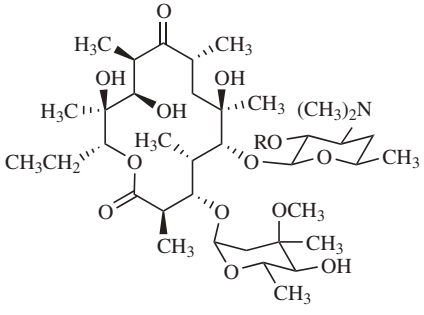
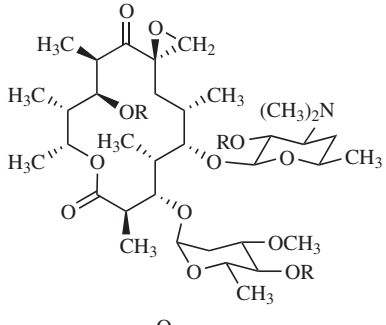
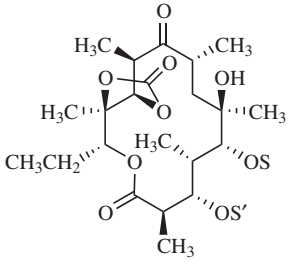


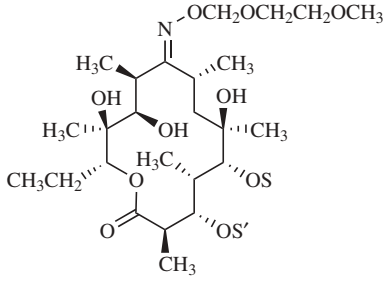
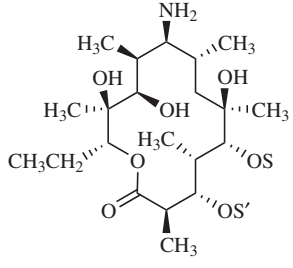
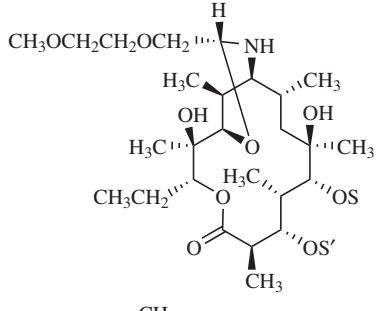
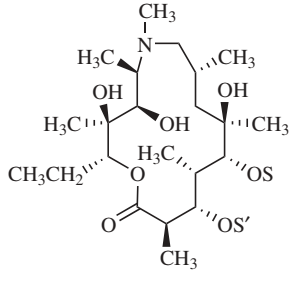
Sporeamicin A	[131418-65-0]	$C_{37}H_{63}NO_{12}C_{36}$-$H_{61}NO_{12}C_{36}H_{61}N$-$O_{12}$	20(R = R′ = CH_3)20(R = H, R′ = CH_3)20(R = CH_3, R′ = H)
Sporeamicin B	[143313-36-4]		
Sporeamicin C	[141340-34-3]		

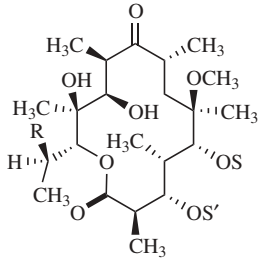
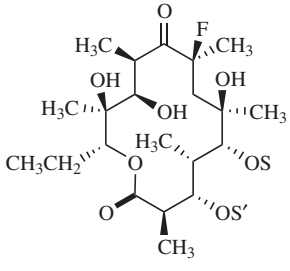
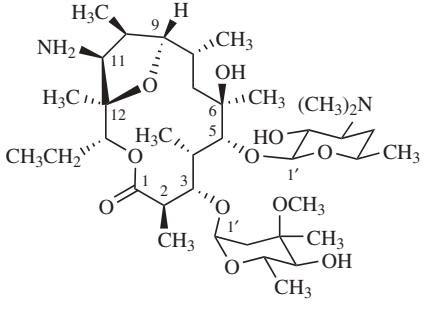


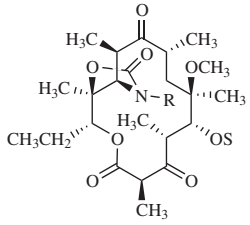
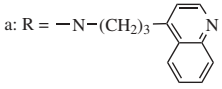
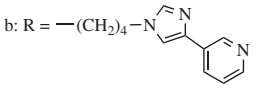
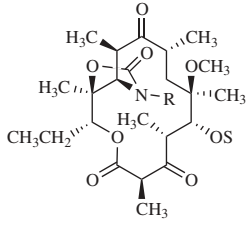
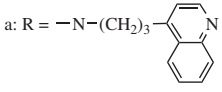
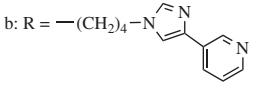
[a]Also known as A1-R6-4.
[b]Also known as XK-41-C.
[c]Also known as XK-41-B_1.
[d]Also known as XK-41-A_2.
[e]Also known as XK-41-A_1.

Table 4. **Derivatives of Erythromycin and Oleandonycin**

Macrolide	CAS Registry Number	Molecular formula	Structure number	Structure
			Erythromycin esters	
2′-*O*-acetylerythromycin	[992-69-8]	$C_{39}H_{69}NO_{14}$	24 (R = $COCH_3$)24 (R =	
2′-*O*-propionylerythromycin	[134-36-1]	$C_{40}H_{71}NO_{14}$	$COCH_2CH_3$)24 (R =	
erythromycin ethyl carbonate	[7218-80-6]	$C_{40}H_{71}NO_{15}$	$COOCH_2CH_3$) 24	
erythromycin ethyl succinate	[1264-62-6]	$C_{43}H_{75}NO_{16}$	(R = $CO(CH_2)_2COOCH_2CH_3$)	
			Other derivatives[a]	
tri-*O*-acetyloleandomycin	[2751-09-9]	$C_{41}H_{67}NO_{15}$	25	
erythromycin-11,12-carbonate	[55224-05-0]	$C_{38}H_{65}NO_{14}$	26	

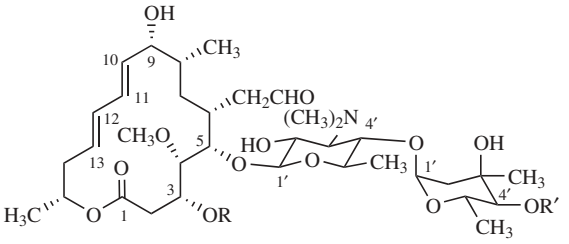
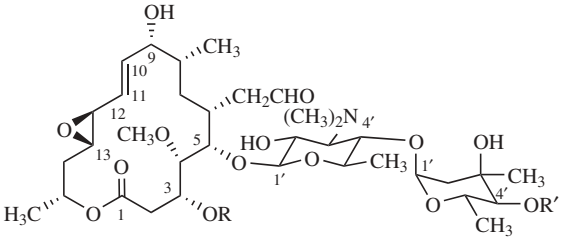
roxithromycin	[80214-83-1]	$C_{41}H_{76}N_2O_{15}$	27	
9(*S*)-erythromycylamine	[26116-56-3]	$C_{37}H_{70}N_2O_{12}$	28	
dirithromycin	[62013-04-1]	$C_{42}H_{78}N_2O_{14}$	29	
azithromycin	[83905-01-5]	$C_{38}H_{72}N_2O_{12}$	30	

clarithromycin	[81103-11-9]	$C_{38}H_{69}NO_{13}$	31	
flurithromycin	[82664-20-8]	$C_{37}H_{66}FNO_{13}$	32	
oxolide	[134060-33-6]	$C_{37}H_{68}N_2O_{11}$	33	

HMR 3004	[172678-62-5]	$C_{43}H_{64}N_4O_{10}$	34a	 
telithromycin	[191114-48-4]	$C_{43}H_{65}N_5O_{10}$	(34b)	
ABT-773	[205110-48-1]	$C_{42}H_{59}N_3O_{10}$	(34c)	  

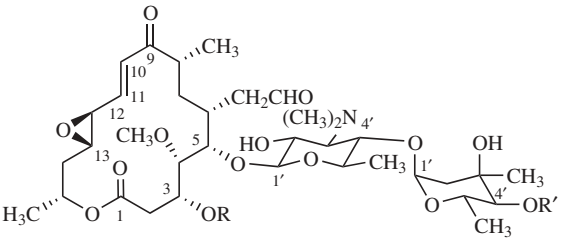
[a]S = desosamine (1, R = OH, R′ = H); S′ = cladinose (8, R = CH_3).

Table 5. **Leucomycins and Related Compounds**

Macrolide	CAS Registry number	Molecular formula	R	R′
Type I: C-9 to C-13 is dienol				
 (**35**)				
leucomycin A_1	[16846-34-7]	$C_{40}H_{67}NO_{14}$	H	isovaleryl
leucomycin A_5	[18361-45-0]	$C_{39}H_{65}NO_{14}$	H	butyryl
leucomycin A_7	[18361-47-2]	$C_{38}H_{63}NO_{14}$	H	propionyl
leucomycin A_9	[18361-49-4]	$C_{37}H_{61}NO_{14}$	H	acetyl
leucomycin V	[22875-15-6]	$C_{35}H_{59}NO_{13}$	H	H
leucomycin A_3(josamycin)	[16846-24-5]	$C_{42}H_{69}NO_{15}$	acetyl	isovaleryl
leucomycin A_4	[18361-46-1]	$C_{41}H_{67}NO_{15}$	acetyl	butyryl
leucomycin A_6	[18361-48-3]	$C_{40}H_{65}NO_{15}$	acetyl	propionyl
leucomycin A_8	[18361-50-7]	$C_{39}H_{63}NO_{15}$	acetyl	acetyl
leucomycin U	[31642-61-2]	$C_{37}H_{61}NO_{14}$	acetyl	H
platenomycin A_1	[40615-47-2]	$C_{43}H_{71}NO_{15}$	propionyl	isovaleryl
midecamycin A_2	[35457-81-9]	$C_{42}H_{69}NO_{15}$	propionyl	butyryl
midecamycin A_1 (espinomycin A_1), (platenomycin B_1)	[35457-80-8]	$C_{41}H_{67}NO_{15}$	propionyl	propionyl
platenomycin C_2 (espinomycin A_3)	[35867-32-4]	$C_{40}H_{65}NO_{15}$	propionyl	acetyl
DHP	[35906-56-0]	$C_{38}H_{63}NO_{14}$	propionyl	H
espinomycin A_2	[40867-12-7]	$C_{42}H_{69}NO_{15}$	propionyl	isobutyryl
platenomycin A_0	[52310-62-0]	$C_{44}H_{73}NO_{15}$	butyryl	isovaleryl
Type II: C-9 to C-13 is epoxyenol				
 (**36**)				
maridomycin I (platenomycin C_3)	[35908-44-2]	$C_{43}H_{71}NO_{16}$	propionyl	isovaleryl
maridomycin VII	[56078-81-0]	$C_{42}H_{69}NO_{16}$	propionyl	butyryl

maridomycin III (platenomycin C_1)	[35775-82-7]	$C_{41}H_{67}NO_{16}$	propionyl	propionyl
maridomycin V	[35942-57-5]	$C_{40}H_{65}NO_{16}$	propionyl	acetyl
maridomycin II (platenomycin C_4)	[35908-45-3]	$C_{42}H_{69}NO_{16}$	acetyl	isovaleryl
maridomycin IV	[35942-56-4]	$C_{40}H_{65}NO_{16}$	acetyl	propionyl
maridomycin VI	[35775-66-7]	$C_{39}H_{63}NO_{16}$	acetyl	acetyl

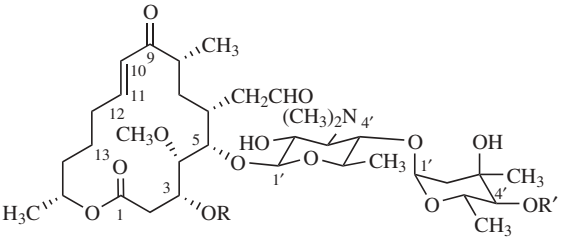
Type III: C-9 to C-13 is epoxyenone



(**37**)

carbomycin A (deltamycin A_4)	[4564-87-8]	$C_{42}H_{67}NO_{16}$	acetyl	isovaleryl
deltamycin A_3	[58880-24-3]	$C_{41}H_{65}NO_{16}$	acetyl	butyryl
deltamycin A_2	[58880-23-2]	$C_{40}H_{63}NO_{16}$	acetyl	propionyl
deltamycin A_1	[58880-22-1]	$C_{39}H_{61}NO_{16}$	acetyl	acetyl
deltamycin X, (EOA)	[40625-70-5]	$C_{37}H_{59}NO_{15}$	acetyl	H
EOP	[41688-43-1]	$C_{38}H_{61}NO_{15}$	propionyl	H

Type IV: C-9 to C-13 is dienone



(**38**)

carbomycin B	[21238-30-2]	$C_{42}H_{67}NO_{15}$	acetyl	isovaleryl
platenomycin W_1	[35867-31-3]	$C_{43}H_{69}NO_{15}$	propionyl	isovaleryl
platenomycin W_2	[52310-61-9]	$C_{44}H_{71}NO_{15}$	butyryl	isovaleryl
niddamycin	[20283-69-6]	$C_{39}H_{63}NO_{14}$	H	butyryl
midecamycin A_4	[36083-82-6]	$C_{42}H_{67}NO_{15}$	propionyl	butyryl
midecamycin A_3	[36025-69-1]	$C_{41}H_{65}NO_{15}$	propionyl	propionyl
DOA	[52278-66-7]	$C_{37}H_{59}NO_{14}$	acetyl	H
DOP	[40580-80-1]	$C_{38}H_{61}NO_{14}$	propionyl	H

Table 6. **Spiramycins**

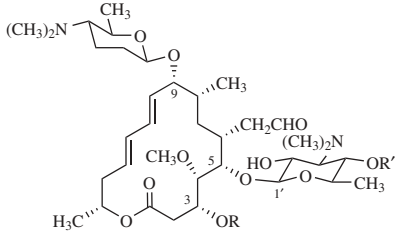
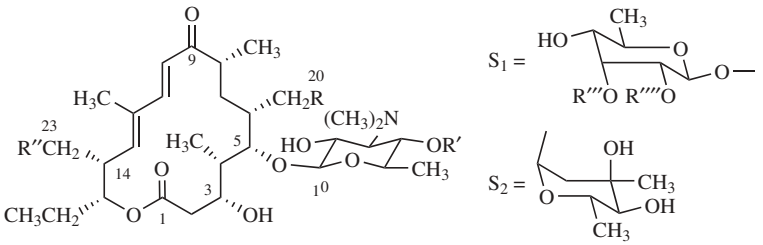
Macrolide	CAS Registry Number	Molecular formula	Structure number	Structure
spiramycin I (foromacidine A)	[24916-50-5]	$C_{43}H_{74}N_2O_{14}$	39(R =H,R′ =mycarosyl)	
spiramycin II(foromacidine B)	[24916-51-6]	$C_{45}H_{76}N_2O_{15}$	39(R =acetyl,R′ =mycarosyl)	
spiramycin III(foromacidine C)	[24916-52-7]	$C_{46}H_{78}N_2O_{15}$	39(R =propionyl,R′ =mycarosyl)	
neospiramycin I	[70253-62-2]	$C_{36}H_{62}N_2O_{11}$	39(R = R′ =H)	

Table 7. **Tylosin and Related Compounds**



(**40**)

Macrolide	CAS Registry number	Molecular formula	R	R′	R″	R‴	R⁗
tylosin	[1401-69-0]	$C_{46}H_{77}NO_{17}$	CHO	S_2	S_1	CH_3	CH_3
relomycin (20-dihydrotylosin)	[62902-06-1]	$C_{46}H_{79}NO_{17}$	CH_2OH	S_2	S_1	CH_3	CH_3
macrocin	[11049-15-3]	$C_{45}H_{75}NO_{17}$	CHO	S_2	S_1	H	CH_3
O-demethylmacrocin	[79404-98-1]	$C_{44}H_{73}NO_{17}$	CHO	S_2	S_1	H	H
desmycosin	[11032-98-7]	$C_{39}H_{65}NO_{14}$	CHO	H	S_1	CH_3	CH_3
lactenocin	[110469-05-1]	$C_{38}H_{63}NO_{14}$	CHO	H	S_1	H	CH_3
O-demethyllactenocin (DOML)	[81557-35-9]	$C_{37}H_{61}NO_{14}$	CHO	H	S_1	H	H
23-*O*-demycinosyltylosin	[79592-92-0]	$C_{38}H_{63}NO_{13}$	CHO	S_2	OH		
23-(demycinosyloxy)tylosin	[79404-97-0]	$C_{38}H_{63}NO_{12}$	CHO	S_2	H		
GS-77-1	[86293-46-1]	$C_{38}H_{65}NO_{11}$	CH_3	S_2	H		
GS-77-3	[81661-90-7]	$C_{38}H_{65}NO_{12}$	CH_3	S_2	OH		

Table 8. **Angolamycin and Related Compounds**

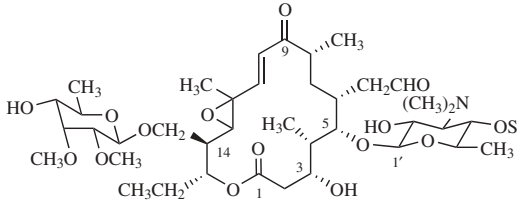
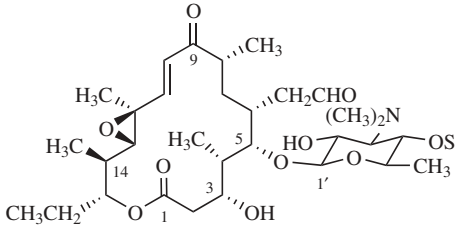
Macrolide	CAS Registry Number	Molecular formula	Structure number	Structure
angolamycin	[1402-83-1]	$C_{46}H_{77}NO_{17}$	41(S = α−L−mycarosyl)	
(shincomycin A) staphcoccomycin	[73047-31-1]	$C_{39}H_{65}NO_{14}$	41(S = H)	
acumycin (cirramycin B)	[25999-30-8]	$C_{37}H_{59}NO_{12}$	42(S = α−L−cinerulosyl)	
cirramycin F-1	[74918-31-3]	$C_{37}H_{61}NO_{12}$	42(S = α−L−rhodinosyl)	
(A6888C)cirramycin	[120851-46-9]	$C_{37}H_{61}NO_{12}$	42(S = α−L−amicetosyl)	
F-2M119-a	[111205-12-0]	$C_{39}H_{65}NO_{13}$	42(S = α−L−cladinosyl)	

Table 9. **Cirramycin A_1, Rosaramicin, and Related Compounds**

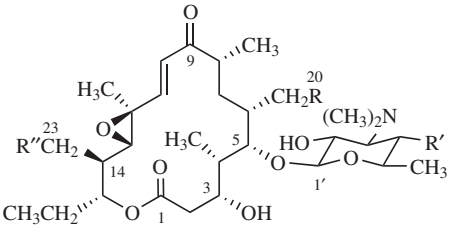
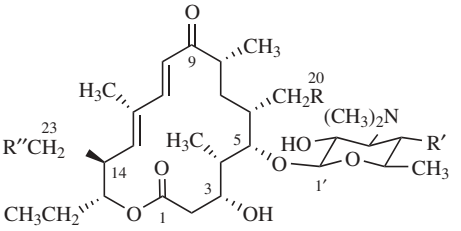
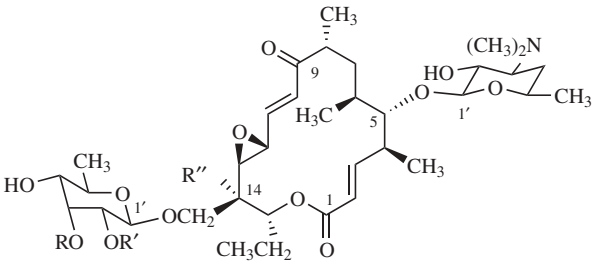
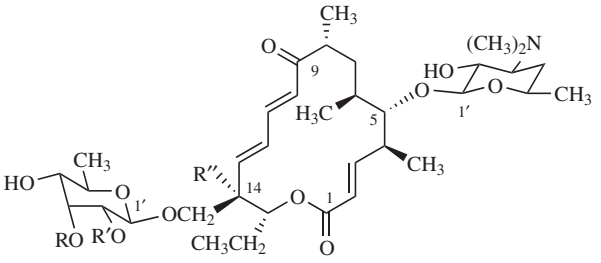
Macrolide	CAS Registry Number	Molecular formula	R	R′	R″
C-9 to C-13, epoxyenone					
					
		(**43**)			
cirramycin A_1	[25339-90-6]	$C_{31}H_{51}NO_{10}$	CHO	OH	H
rosaramicin	[35834-26-5]	$C_{31}H_{51}NO_9$	CHO	H	H
izenamicin A_3	[86132-03-8]	$C_{31}H_{51}NO_{10}$	CHO	H	OH
juvenimicin A_4	[61475-37-4]	$C_{31}H_{53}NO_9$	CH_2OH	H	H
M-4365 A_1	[59227-84-8]	$C_{31}H_{53}NO_8$	CH_3	H	H
juvenimicin A_2	[61417-47-8]	$C_{30}H_{51}NO_8$	H	H	H
C-9 to C-13, dienone					
					
		(**44**)			
5-*O*-mycaminosyltylonolide (OMT)	[61257-02-1]	$C_{31}H_{51}NO_{10}$	CHO	OH	OH
23-deoxy-5-*O*-mycaminosyl tylonolide (DOMT)	[115033-64-2]	$C_{31}H_{51}NO_9$	CHO	OH	H
izenamicin B_3	[80240-61-5]	$C_{31}H_{51}NO_9$	CHO	H	OH
M-4365 G_2	[56689-42-0]	$C_{31}H_{51}NO_8$	CHO	H	H
juvenimicin B_3	[61417-48-9]	$C_{31}H_{53}NO_9$	CH_2OH	H	OH
juvenimicin B_1	[58947-83-4]	$C_{31}H_{53}NO_8$	CH_2OH	H	H
GS-77-4	[80830-18-8]	$C_{31}H_{53}NO_9$	CH_3	OH	OH
GS-77-2	[80830-17-7]	$C_{31}H_{53}NO_8$	CH_3	OH	H
M-4365 G_1	[59227-83-7]	$C_{31}H_{53}NO_7$	CH_3	H	H
izenamicin B_2	[86131-94-4]	$C_{30}H_{51}NO_8$	H	H	OH

Table 10. **The Mycinamicins**

Macrolide	CAS Registry Number	Molecular formula	R	R′	R″
C-9 to C-13, epoxyenone					
 (**45**)					
mycinamicin I	[73665-15-3]	$C_{37}H_{61}NO_{12}$	CH_3	CH_3	H
mycinamicin II (miporamicin)	[73684-69-2]	$C_{37}H_{61}NO_{13}$	CH_3	CH_3	OH
C-9 to C-13, dienone					
 (**46**)					
mycinamicin III	[73684-70-5]	$C_{36}H_{59}NO_{11}$	H	CH_3	H
mycinamicin IV	[73684-71-6]	$C_{37}H_{61}NO_{11}$	CH_3	CH_3	H
mycinamicin V	[73684-72-7]	$C_{37}H_{61}NO_{12}$	CH_3	CH_3	OH
mycinamicin VI	[85687-36-1]	$C_{35}H_{57}NO_{11}$	H	H	H
mycinamicin VII[a]	[77704-58-6]	$C_{29}H_{47}NO_7$			H

[a]Mycinamicin VII has a hydrogen where the sugar is at the C-14 position.

Table 11. **Chalcomycin, Aldgamycin, and Related Compounds**

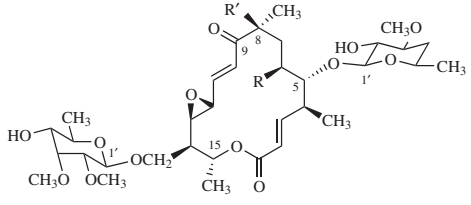
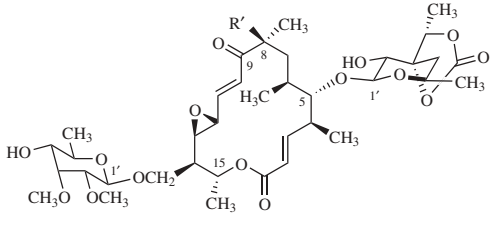
Macrolide	CAS Registry number	Molecular formula	Structure number	Structure
chalcomycin	[20283-48-1]	$C_{35}H_{56}O_{14}$	47(R =CH_3,R′ =OH)	
neutramycinCP-70,662	[1404-08-6]	$C_{34}H_{54}O_{14}$	47(R =H,R′ =OH)	
	[125225-83-4]	$C_{35}H_{56}O_{13}$	47(R =CH_3,R′ =H)	
aldgamycin Faldgamycin	[55141-41-8]	$C_{37}H_{56}O_{16}$	48(R =OH)48	
G (8-deoxyaldgamycin F)	[107745-56-2]	$C_{37}H_{56}O_{15}$	(R =H)	

Table 12. **Tylosin-Type Aglycones**

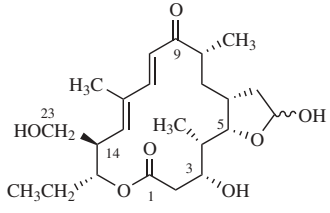
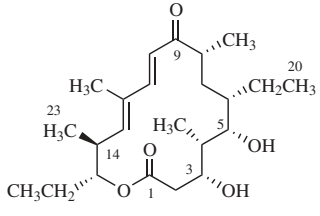
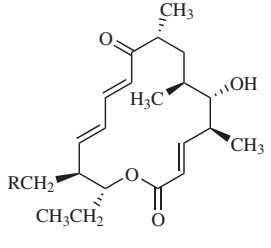
Macrolide	CAS Registry number	Molecular formula	Structure number	Structure
tylonolide	[61219-81-6]	$C_{23}H_{36}O_7$	49	
tylactone (protylonolide)	[74758-60-4]	$C_{23}H_{38}O_5$	50	
mycinolide IV protomycinolide IV	[77704-61-1] [79495-87-7]	$C_{21}H_{32}O_5$ $C_{21}H_{32}O_4$	51,(R =OH) 51(R =H)	

Table 13. **Selected Commercial Macrolide Products for Human Medicine**

Clinical Macrolides[a]	Trade name[b]	Route	Manufacturer
erythromycin (enteric coated tablets)	Ery-Tab	oral	Abbott
erythromycin (film coated tablets)	Erythromycin Base Filmtab	oral	Abbott
erythromycin (polymer coated particles)	PCE Dispertab	oral	Abbott
erythromycin (enteric coated pellets)	Erythromycin Delayed-Release Capsules	oral	Abbott
erythromycin (enteric coated pellets)	Eryc Delayed Release Capsules	oral	Warner Chilcot
erythromycin topical solution	Theramycin Z	topical	Bioglan
erythromycin topical gel	Emgel	topical	Glaxo Wellcome
erythromycin topical ointment	Akne-Mycin	topical	Healthpoint
erythromycin ophthalmic ointment	Ilotycin ointment	topical	Dista
erythromycin + benzoyl peroxide gel	Benzamycin	topical	Dermik
erythromycin stearate	Erythrocin stearate	oral	Abbott
erythromycin stearate	Erythromycin stearate	oral	Mylan
erythromycin lactobionate	Erythromycin lactobionate.	i.v.	Lederle
erythromycin lactobionate	Erythrocin lactobionate	i.v.	Abbott
erythromycin gluceptate	Ilotycin glucoheptonate	i.v.	Dista
erythromycin ethylsuccinate	E.E.S.	oral	Abbott
erythromycin ethylsuccinate	EryPed	oral	Abbott
erythromycin ethylsuccinate	Erythromycin ethylsuccinate	oral	Mylan
erythromycin ethylsuccinate + sulfisoxazole acetyl	Erythromycin ethylsuccinate + sulfisoxazole acetyl	oral	Lederle
clarithromycin	Biaxin	oral	Abbott
azithromycin	Zithromax	oral	Pfizer
	Sunamed (Yugoslavia)	oral	Pliva
dirithromycin	Dynabac	oral	Sanofi
roxithromycin	Rulid (France)	oral	HMR
flurithromycin ethylsuccinate	Flurizic (Italy)	oral	Pierrel
erythromycin-11,12-carbonate	Davercin (Poland)	oral	Tarchomin
erythromycin estolate	Ilosone	oral	Dista
erythromycin acistrate	Erasis (Finland)	oral	Orion
erythromycin stinoprate	Eritrocist (Italy)	oral	Edmond Pharma
Triacetyloleandomycin	TAO	oral	Roerig
spiramycin	Rovamycine (France)	oral	RPR
josamycin	Josamycin (Japan)	oral	Yamanouchi
midecamycin	Medemycin (Japan)	oral	Meiji Seika
miokamycin	Miocamycin (Japan)	oral	Meiji Seika
rokitamycin	Ricamycin (Japan)	oral	Toyo Jozo
telithromycin (pending)	Ketek (proposed)	oral	Aventis

[a]Abstracted from Refs. 483–485.

[b]Country in parenthesis represents launch outside the United States.