Recent Advances in the Field of 16-Membered Macrolide Antibiotics

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Abstract: The continuing emergence of bacterial resistance has provided an incentive for recent intensified research on macrolide antibiotics. Belonging to the macrolide family, 16-membered macrolides also experience a renewed interest in further exploration. The medicinal potential of 16-membered macrolides in search for new antibacterials stems from some advantages over 14-membered macrolides, such as gastrointestinal tolerability, structural flexibility, and lack of inducible resistance. Thus, compared with abundant articles on various 14-membered macrolide derivatives in the literature, this review will highlight some representative 16-membered macrolide antibiotics and their recently discovered analogs. Furthermore, the action and resistance mechanisms of 16-membered macrolide antibiotics will be elucidated as well to assist the drug design.

Keywords: 16-membered macrolides, structural flexibility, mycarose moiety, antimicrobial properties, resistant strains, resistance mechanism, tylosin, leucomycin.

INTRODUCTION

As a large family of both natural and semisynthetic antibiotics, macrolides are characterized by a 14-, 15- or 16-membered lactone ring, to which one or more deoxy sugars were attached. Compared with penicillin, the macrolide class of antibiotics exhibits a favorable tolerance among the young and elderly, which made them the most common used antibiotics against bacterial infections. Unfortunately, the clinically extensive acceptance of macrolides has led to a rapid increase in the rate of bacterial resistance since 1990s. Against resistant strains of bacteria, none of the marketed macrolides demonstrated a preferable efficacy. Thus, the search for novel macrolide-derived antibacterials with broader spectrum of activity has been a constant goal for medicinal chemists [1]. However, since the discovery of the first macrolide, known as erythromycin A (**1**), tremendous efforts have been undertaken on the structural derivatization of the 14-membered macrolides and exploration of novel 16-membered macrolides has been only minimally carried out.

On the other hand, in contrast to the 14-membered macrolide antibiotics, 16-membered macrolides show some preferable advantages, such as gastrointestinal tolerability, structural flexibility and lack of inducible resistance [2], and development for the 16-membered macrolides has been the new hot spot. Now, the 16-membered macrolides have been another large and important family of macrolide antibiotics [3].

The first member of 16-membered macrolides named carbomycin (**2**) was discovered in 1952. Since then, many series of 16-membered macrolide derivatives have been prepared, such as spiramycin (**3**), tylosin (**4**), leucomycin (**5**) and midecamycin (**6**). Studies have suggested that the ability to induce resistance was linked to the structure at the C-3 position. The 16-membered macrolides lack inducible resistance likely due to the loss of cladinose moiety at their C-3 position. The 16-membered macrolides all have a disaccharide or monosaccharide at the C-5 position of the lactone ring and are traditionally divided into sub-families based upon the substitution patterns of their aglycones. The principal prototypes of this family can be represented by spiramycin, leucomycin, and tylosin [4]. The modifications of the 16-membered macrolides often focus on the different sugars. The purpose of these researches is to improve the pharmacokinetic profiles and metabolism of these derivatives [5]. For example, it could be an innovative starting point for further modifications to enhance its antibacterial activity and acid stability by removing the acid labile mycarose sugar from tylosin [6].

In consideration of the medicinal potential stated above, the aim of this review is to update our knowledge of 16-membered macrolides investigated in recent years, and give an account for the current understanding of the mechanism of action and resistance of 16-membered macrolides, which is a driving force for creation of structurally diverse antibiotics with the potential of enhanced biological activity.

THE MECHANISMS OF ACTION OF 16-MEMBERED MACROLIDES

A number of nucleotide residues in domain V of 23S rRNA interact with the macrolide molecule. A macrolide molecule is coordinated in its binding site by multiple hydrophobic, hydrogen bonds (and possibly, a covalent bond in case of some 16-membered macrolides) between its functional groups and 23S rRNA [1]. The 16-membered macrolides bind at overlapping sites, in the central loop region of domains II and V of 23S rRNA, which were investigated by biochemical and genetic methods. They inhibit protein synthesis by binding to 50S subunit of

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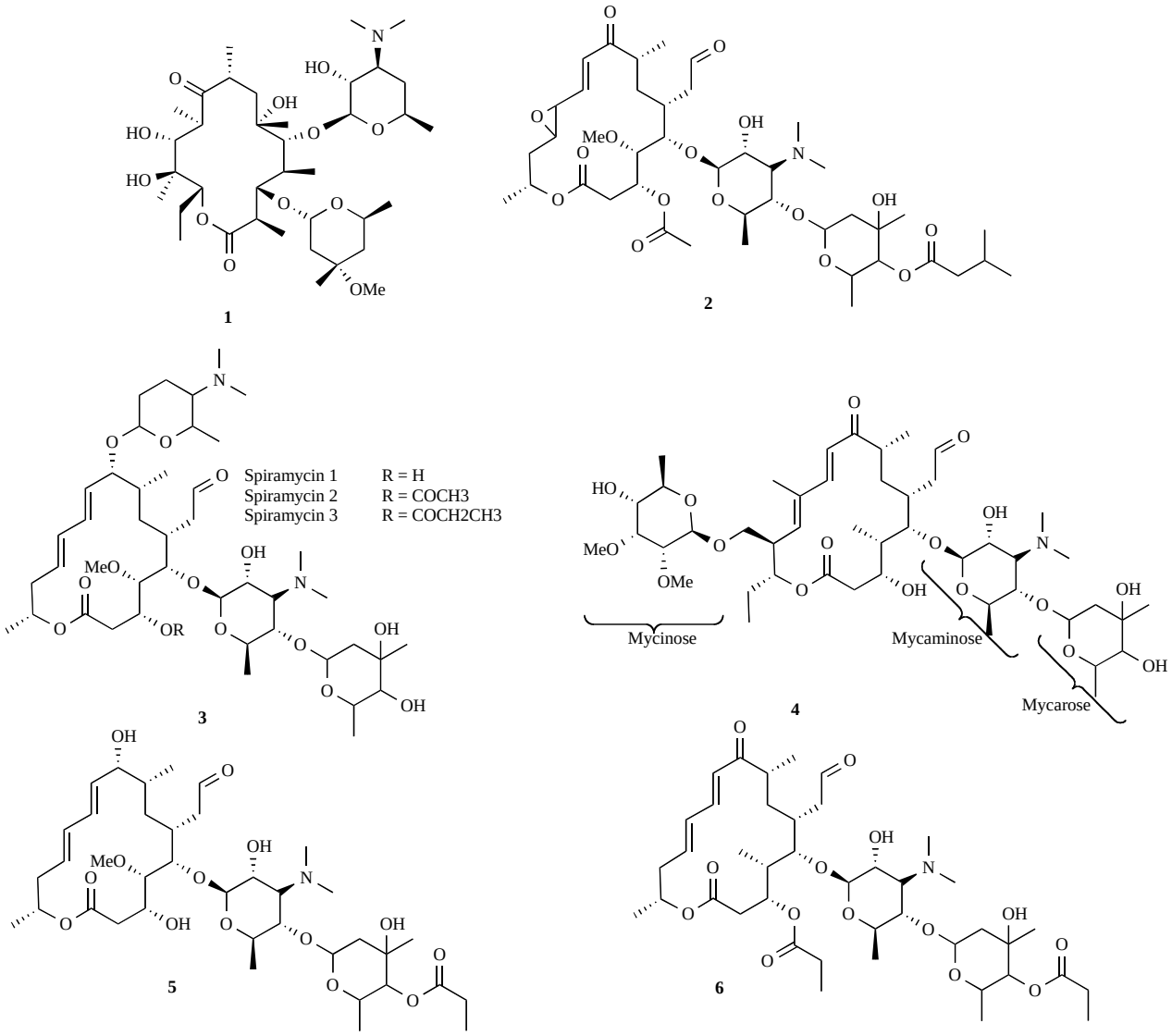

Fig. (1). Erythromycin A (**1**), carbomycin (**2**), spiramycin (**3**), tylosin (**4**), leucomycin (**5**) and midecamycin (**6**).

bacterial ribosomes or affecting the peptidyl transferase reaction [5]. It has been shown that the antibacterial activity might depend on the nature and the length of the peptidyl moiety of the donor substrate [7].

Compared with the 14-membered macrolides, all 16-membered macrolides share a larger lactone ring. The additional two atoms seem to be allowed for higher conformational flexibility and also provide more potential interactions with the ribosome. Weisblum also noted that the 16-membered macrolides such as carbomycin, niddamycin and tylosin bind selectively to protein L27, whereas erythromycin, a 14-membered macrolide, does not bind to the protein L27. These observations show consistency between macrolide ring size and ability to bind to L27 and also reflect the similar affinity of the larger macrolides to L27 [8].

On the other hand, the role and the importance of the different sugar substituents especially the amino sugars in the 16-membered macrolides have been investigated in the further study [9]. The 16-membered macrolides, exemplified by carbomycin, spiramycin, and tylosin, possess an additional mycarose moiety in the C-5 disaccharide of the lactone ring. The presence of mycarose could confer an interaction with the center of peptidyl-transferase, thereby interfering with peptide-bond formation by binding to the A site and blocking the binding of amino acyl tRNA [10]. In contrast, the molecules, containing a monosaccharide at the C-5 position of the lactone ring (e.g., desmycosin and chalcomycin) [5], do not inhibit the peptidyl transferase reaction [11].

Generally speaking, the common binding site of 16-membered macrolides has A2058, A2059 and A2062 similar to that of 14-membered macrolides. In addition to main binding site A2058, some 16-membered macrolides also bind to U2506 which depends on the mycarose moiety. For example, spiramycin and desmycosin were found to protect A2058, A2059, A2062 and U2609 [5], and chalcomycin to protect A2058 and A2059 [12]. Tylosin also protected nucleotide A752 (in domain II) [10].

THE RESISTANCE MECHANISMS OF 16-MEMBERED MACROLIDES

The present studies have shown that several various ribosomal mutations can lead to macrolide resistance. Resistance to macrolides is increasingly reported in clinical isolates of *Streptococcus pneumoniae* worldwide. *Streptococci,* as opposed to *Staphylococci*, are cross-resistant to 14- to 16-membered macrolide antibiotics whether resistance is inducible or constitutive [13]. It is important for us to understand the macrolide resistance to control and prevent the spread of macrolide-resistant strains [14]. DNA-based techniques, especially PCR and real-time PCR, are often used to examine resistant genes in microbial communities [15]. Typically, resistance to macrolides including 14- to 16-membered macrolides, is acquired through either target site modification (target site alteration, methylation or mutation of nucleotides involved in drug binding) or active efflux [16].

Altered Target Site: Ribosomal Proteins

Ribosomal mutation has been reported only recently in a few clinical isolates of *S. pneumoniae*. Mutations conferring resistance to macrolides were first identified in proteins L4 and L22 of *E. coli*, and subsequently in 23S rRNA. Ribosomal proteins L4 and L22 are involved in the binding of macrolides to the 50S subunit of the ribosome [17]. L4 plays an important role in the maintenance of the ribosome structure. The L4 protein mutations occur in a region of 32 amino acids highly conserved in various species and interfere with the binding of the protein to rRNA [18].

Berisio *et al.* noted that domain II and protein L22 can stabilize the binding of the 16-membered macrolides with a mycinose sugar at position 14, the mycinose sugar can serve as an additional interacting moiety. The L22 deletion causes alterations in the tunnel cross-section and eliminates possible direct drug-ribosome interactions, thus portraying the way that the L22 deletion exerts its effects in the presence of a mutated 2058A [16].

Methylation

The 23S rRNAs of Gram-positive bacteria appear to lack any N^6-methylated adenine unless the cells are resistant to MLS (macrolide–lincosamide–streptogramin) antibiotics by the methylase mechanism. The *erm* genes encode 23S rRNA adenine-specific N^6-methyl transferases, which methylate the 23S rRNA of bacteria [15]. Expression of an *erm*-resistant determinant in bacteria results in production of a methyl transferase which modifies the key nucleotide A2058, thereby conferring resistance to macrolides. The ring size is a major factor to induce resistance, therefore 16-membered macrolides are weak inducers [19]. Studies have suggested that macrolides bearing the C-3 cladinose induce resistance. Because the 16-membered macrolides lost the cladinose moiety, they have weak capabilities to induce resistance.

Nucleotide Mutations

A clinical isolate with an A2062C mutation confirmed that the binding sites of 14- and 16-membered macrolides are distinct [20]. The A2062C mutation in 23S rRNA has been found to be associated with 16-membered macrolide and streptogramin resistance in *Streptococcus pneumonia* [17].

The mutation A2058C results in a significant resistance to spiramycin, josamycin, and carbomycin, but it has only a small effect on the interactions of tylosin and desmycosin with the ribosome. The A2058G mutation is associated with resistance to 14-to 16-membered macrolides in a number of bacteria including *B. pilosicoli* and is likely to be responsible for spiramycin resistance in *T. pallidum* [21]. *Mycoplasma pneumoniae* displays similar phenotypes to *H. pylori* containing A2058G and A2059G mutations [17], and it has been shown that the A2059G mutation confers a high level of resistance to erythromycin, azithromycin, and 16-membered macrolides, especially tylosin and spiramycin [22]. The double mutation 2058G/2059G results in a high-level resistance to all ketolides and 16-membered macrolides [8]. These results described above could demonstrate subtle differences in the mode of interaction of 14- and 16-membered macrolides with the 2058 region of 23S rRNA.

With the emergence of new resistance mechanisms, it seems advisable to test *in vitro* activity of each member of the 14- to 16-membered macrolides.

Active Efflux

Efflux pumps such as *Mef* in *streptococci* and *Msr* in *staphylococci* and *enterococci* are specific for the export of macrolides. An advantage to the 16-membered macrolides is that they are not susceptible to *mef* (A)- and *msr* (A)-mediated efflux, such as miokamycin (MOM) and rokitamycin (RKM) [2]. The *mef* gene is the most common macrolide resistance determinant among *S. pneumoniae* isolated in the United States. Bacteria carrying the gene encoding macrolide efflux (i.e. the *mef* E gene) display relatively low-level resistance [23]. The efflux phenotype *mef* (A) is characterized by resistance to 14-membered and 15-membered macrolides only [18].

REPRESENTATIVE DRUGS

In recent years, a dramatic increase of antibiotic resistance has been observed [24], which urges the rapid development of new, more potent drugs and will hopefully lead to the widespread application of new antibiotics in the future [25]. In particular, keto-derivatives of 14- and 16-membered macrolides have emerged as key intermediates for the synthesis of a large variety of biologically active natural product derivatives [25].

Tylosin and its Derivatives

Tylosin and Desmycosin

Tylosin, the fermentation product of *Streptomyces fradiae* NRRL2702 [26], is commonly used for therapeutic treatment and prophylaxis in livestock. In U.S. agriculture, tylosin accounts for as much as 5% of the total antibiotic consumption [27]. Tylosin was reported as early as in 1970 to control AFB (American foulbrood). It has been shown that tylosin is highly effective in controlling active AFB infections, with low acute toxicity for honey bee larvae and adults. Desmycosin (**7**) (also referred to as tylosin B) has been identified as the primary degradation product of tylosin in honey [28].

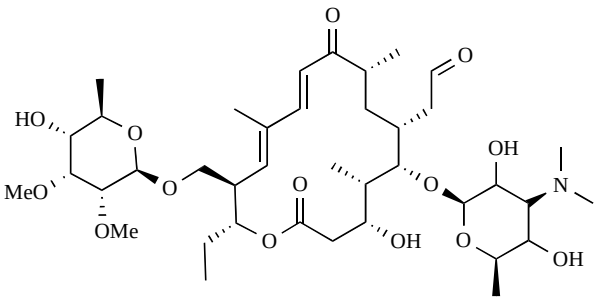

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Fig. (2). Desmycosin (**7**).

Tylosin has activity against Gram-positive bacteria and can be either bactericidal or bacteriostatic depending on the dose and susceptibility of the specific organism [27]. It was comparable in its effectiveness at a significantly lower concentration compared with spiramycin. Stakenborg showed that the MICs (minimal inhibitory concentration) for tylosin ranged from 8 to 16 μg/mL for the resistant strain and from 0.03 to 0.125 μg/mL for the five susceptible strains [29].

Tylosin possesses a highly substituted aglycone (tylonolide) with two double bonds and a third saccharide substituent (β-D-mycinose) in addition to a disaccharide attached to the C-5 hydroxyl group [4]. Compared with erythromycin, tylosin has a hydroxyl group instead of a neutral sugar at C-3 position, and a side-chain sugar at C-14 position [30]. Susan et.al noted that the mycarose moiety of tylosin is important for inhibition of cell-free protein synthesis [5].

Aivlosin

Several semisynthetic derivatives within this family have been commercially developed, two of which have been introduced as new veterinary antibiotics. A series of 3, 4″−ester derivatives of tylosin was prepared by bioconversion methods. From this series, 3-*O*-acetyl-4"-*O*-isovaleryl-tylosin (**8**) (Aivlosin, AIV-tylosin) was selected for commercial development as a new veterinary antibiotic to treat *Mycoplasma pneumonia* in swine and poultry [4].

Tilmicosin

The second new macrolide is tilmicosin (**9**), which originated from a SAR (structure-activity relationship) study of tylosin derivatives and has exhibited an improved oral efficacy and bioavailability. As a result of long half-life, tilmicosin is effective for the treatment of respiratory disease in cattle [4].

Both tilmicosin and tylosin have a dimethyl amino group on the amino sugar (desosamine) attached to the C-5 position, and this group plays an important role in increasing the potency of motilides. The major findings from Nouri *et al*'s studies [30] were that tylosin and tilmicosin increased the abomasal emptying rate in suckling calves. Their findings are contrary to long-held beliefs that 16-membered macrolides (such as tylosin and tilmicosin) have no motilide activity.

The traditional method of tilmicosin synthesis starts with the removal of the sugar mycarose from the product of tylosin. It can also be produced by fermentation of *Streptomyces fradiae*. Min *et al.* described the application of the modified gene disruption method in the in-frame deletion of the *tylCV* gene in *S. fradiae* for the generation of a high desmycosin producer, which could be scale-up for industrial fermentation for semi-synthesis of tilmicosin directly. In other words, the direct precursor of tilmicosin is desmycosin [13]. Compared with the traditional method, using fermented

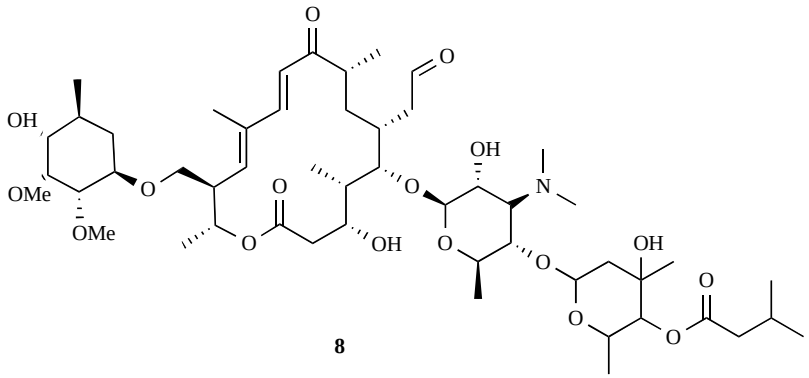

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Fig. (3). 3-*O*-Acetyl-4″-*O*-isovaleryl-tylosin (**8**).

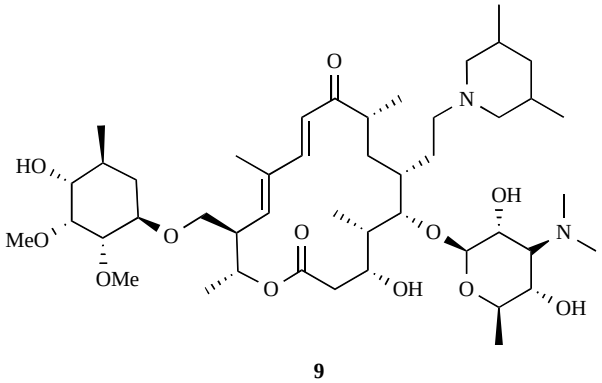

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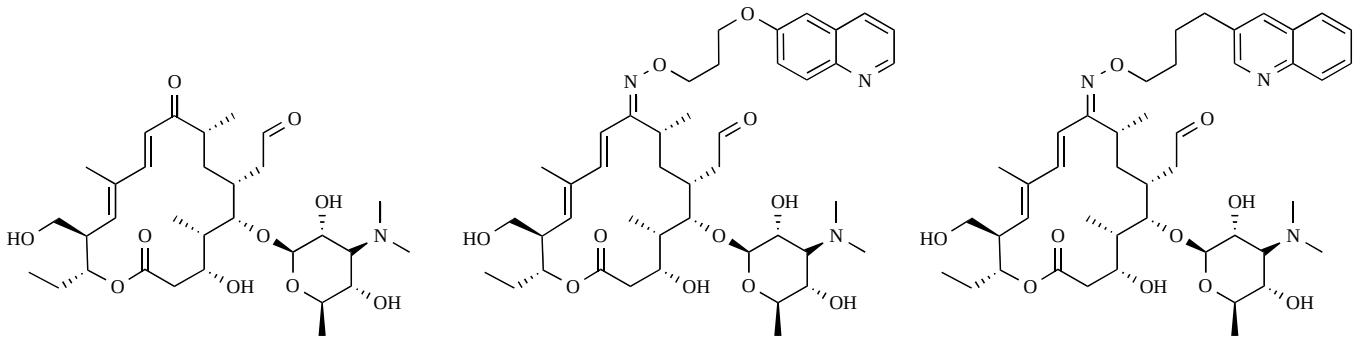
Fig. (4). Tilmicosin (**9**).



10 **10a** **10b**

Fig. (5). 5-*O*-Mycaminosyltylonolide (OMT) (**10**), OMT derivatives (**10a**) and (**10b**).

desmycosin as the direct precursor will be simpler and more efficient, and it could be applied in the industrial production of tilmicosin.

5-*O*-Mycaminosyltylonolide (OMT) and Derivatives

*OMT and 9-*O*-Arylalkyloxime Derivatives*

5-*O*-Mycaminosyltylonolide (OMT) (**10**) is a precursor in the biosynthesis of the macrolide tylosin, which is a new 16-membered 9-aryl-alkyloxime derivative.

Fu *et al.* used OMT as the starting compound and introduced alkylaryl linkers of varying length at the C-9 position of its lactone ring for OMT analogs. Many of the arylalkyloxime OMT analogs have comparable or better activity than that of EMA or OMT against the macrolide-susceptible strains such as *S. pneumonia* ATCC700671, *Staphylococcus aureus* ATCC29213, and *Staphylococcus epidermidis* ATCC12228. These analogs showed substantially an improved potency against a number of macrolide-resistant strains of *S. pneumonia* (0.025 μg/mL) [31]. It is noteworthy that the compounds **10a** and **10b** with a side-chain linker length of four atoms are known to be more effective against macrolide resistant strains than OMT, while **11a** and **11b** exhibited reduced antibiotic activity compared to OMT. The introduction of aromatic side chains to 20-deoxy-20-(3,5-dimethyl-1-piperidin-1-yl)-OMT-9-oxime restored antibacterial activity only slightly. And subsequently, Karahalios *et al.* [32] showed that the binding site of the lactone ring of OMT, **10a**, and **10b** is likely to be similar to that of other 16-membered macrolides, such as tylosin. These compounds were found to exhibit high activity against macrolide-resistant strains.

4′-Substituted 16-Membered Macrolides

Phan [33] reported the synthesis of a series of novel 4′-substituted 16-membered macrolides against constitutively resistant bacteria. The most active compounds (**12a** and **12b**) were obtained when a 3-quinolyl group was attached to the allyl ether at the 4′-position.

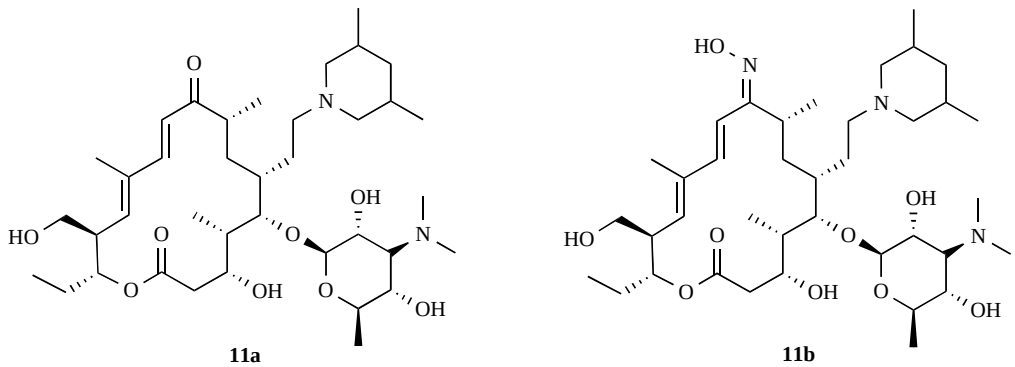
CP-163505

More recently, an extensive series of semisynthetic derivatives has been prepared by reductive amination of rosaramicin and repromicin. Among them, optimized CP-163505 (**13**) has activity against *Pasteurella* species [4], which has been selected for further investigation. Also it was reported that a single 5 mg/kg dose administered subcutaneously was found to control induced pasteurellosis in murine, and induced respiratory diseases in cattle [7].

Leucomycin and its Derivatives

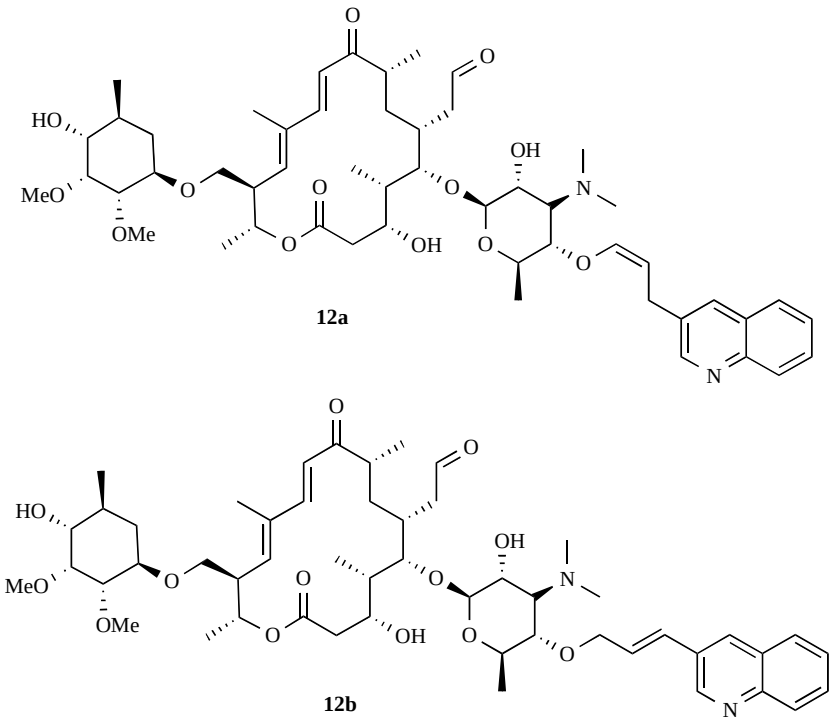
Leucomycin

A second generation of erythromycins, as well as tylosin derivatives used in veterinary medicine has emerged from various synthetic approaches. Important examples are represented by amines (e.g., dirithromycin), oximes (e.g., roxithromycin), amides, and azalides (e.g., azithromycin) [25]. However, many more carbonyl reactions are conceivable, and yet analogs of 16-membered macrolides,



11a **11b**

Fig. (6). OMT derivatives (**11a**) and (**11b**).



12a

12b

Fig. (7). OMT derivatives (**12a**) and (**12b**).

such as the leucomycines, are only relatively little explored [34].

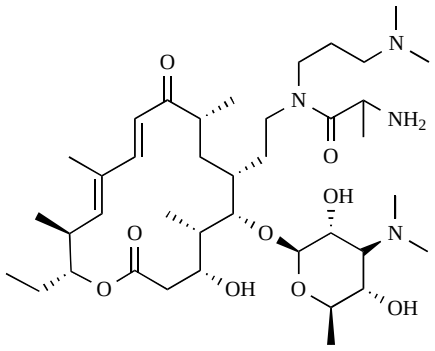


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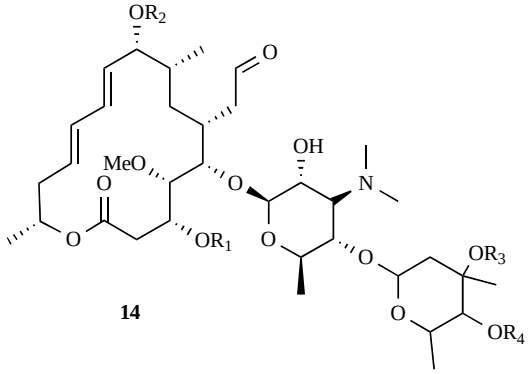
Fig. (8). CP-163505 (**13**).

RKM and MOM

Among the newer commercial compounds, RKM (**14a**) and MOM (**14b**) are semisynthetic acyl derivatives of the leucomycin subfamily, and some research effort on further derivatization of compounds within the leucomycin subfamily of 16-membered macrolides still continues. These two semisynthetic 16-membered macrolide antibiotics have been already proven to be safe in clinical use. Thus, drug discovery in the field of 16-membered macrolides is important for anti-infective chemotherapy in the future [35].

The success of RKM has prompted the synthesis of other 9-oxime derivatives of erythromycin. It was reported that several other new 3″ and/or 4"-*O*-alkyl derivatives exhibited good efficacy and pharmacokinetics in mice, compared to the unsubstituted parent macrolides. The most active derivative in the series was identified as 3″-*O*-methyl-4″-*O*-(3-methylbutyl) leucomycin V (**14c**) [36].



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	R_1	R_2	R_3	R_4
14a	H	H	COEt	CO^nPr
14b	COEt	Ac	Ac	COEt
14c	H	H	Me	$CH_2CH_2CH(CH_3)_2$

Fig. (9). RKM (**14a**), MOM (**14b**) and 3″-*O*-methyl-4″-*O*-(3-methylbutyl) leucomycin V (**14c**).

Josamycin

Josamycin (**15**) is one of the members of leucomycins [6]. Guggenbichler *et al.* found that josamycin showed the high anti-staphylococcal activity. The therapeutically relevant concentrations of josamycin range between 1 and 4 mg/L. Josamycin is still active in *in vitro* against more than 50% of erythromycin-resistant strains of *S. aureus* [37]. This drug is also more active than RKM and CAM (clarithromycin) against erythromycin-resistant *S. aureus*.

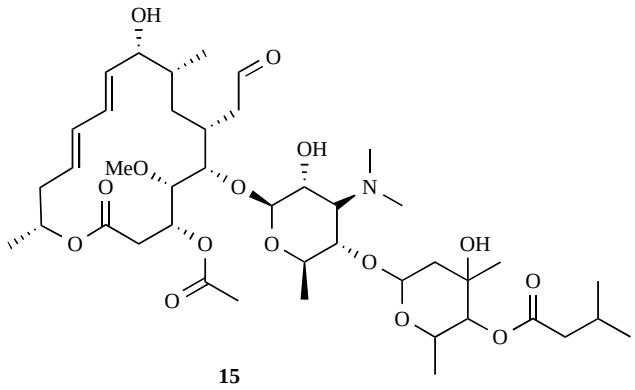

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Fig. (10). Josamycin (**15**).

4′-Substituted Leucomycin

Wang *et al*. reported the synthesis of a series of novel 4′-substituted 16-membered macrolides derived from leucomycin complex. The new 16-membered macrolide antibiotics were tested against resistant bacterial strains (*Streptococcus pyogenes* 1323 and *S. pneumoniae* 7701) and compound **16** showed an enhanced MIC activity [33]. And they proposed that the acid labile mycarose sugar of leucomycins replaced with other substituents would improve their acid stability and increase their binding interactions with the ribosome as well.

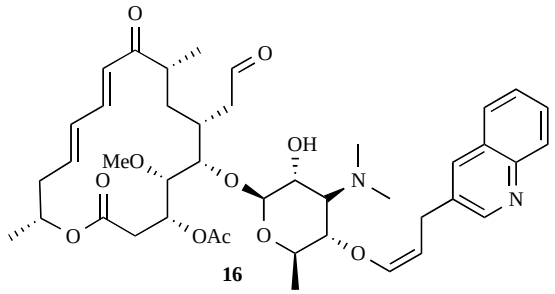

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Fig. (11). 4″-Substituted leucomycin (**16**).

C-18 Aromatic Substituted Leucomycin

Gebhardt *et al*. have synthesized several derivatives of leucomycin A_7 (**17**) by zinc chloride mediated reductive amination of aromatic substituents at the C-18 position, which render the molecules more bulky and lipophilic [34]. Although the antibacterial activity is lower than the native macrolides, their results clearly indicated that the aldehyde function was not essential for bioactivity and even bulky substituents were tolerated at C-18 aldehyde moiety.

3-O-Substituted Analogs of Leucomycin A_7

Furuuchi *et al.* synthesized 3-*O*-substituted analogs of three key 16-membered macrolides in their research, and successfully improved both antibacterial activity and biological stability. They also found that a quinoline side chain in 3-*O*-[(2-quinolyl) carbonyl] leucomycin A_7 (**18**) was executive to overcome resistance of *S. pneumoniae* [35]. Most of the derivatives exhibited stronger antibiotic activities than leucomycin A_7 as expected.

Spiramycin and its Derivatives

Spiramycin

The other major subfamily of 16-membered macrolides is represented by spiramycin produced by *Streptomyces ambofaciens*, the structures of which are shown above. To study metabolic behaviors of the antibiotics in animals, radioactive spiramycins have been prepared by biosynthetic means [38]. Spiramycin is an effective inhibitor of translation and has been used clinically in certain situations.

The spiramycin complex is structurally related to the leucomycins, but is distinguished by the additional amino sugar, β-D-forosamine, attached to the C-9 hydroxyl group of the aglycone and a disaccharide is frequently glycosylated at the C-5 position in structure. The complex is a mixture of three closely related antimicrobial substances, spiramycin I, II and III. Spiramycins II and III are the ethanoate and propanoate esters of spiramycin I at the C-3 position of the lactone ring. It was assumed that the 3-*O*-acetyl group played an important role in influencing the rate of hydrolysis of the lactone moiety of spiramycins.

4"-O-Acetylspiramycin II

Inoue observed that [38] although 4"-*O*-acetylspiramycin II (ASPM) (**19**) maintained its initial antimicrobial activity in liver homogenate, the apparent stability of ASPM was due to the antibacterial activity of SPM-II, which is more potent in

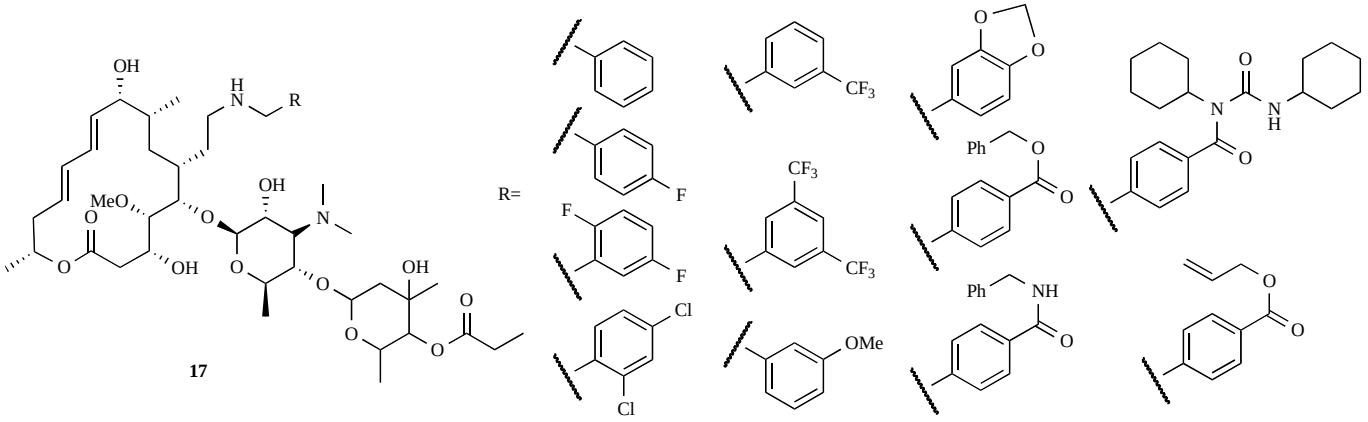

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Fig. (12). C-18 Aromatic substituted analogs of leucomycin A_7 (**17**).

in vitro than ASPM. The 4"-*O*-acetyl group of ASPM was removed from liver to give more potent SPM-II.

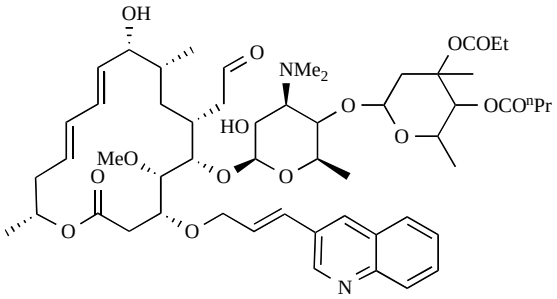

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Fig. (13). 3-*O*-Substituted leucomycin A_7 (**18**).

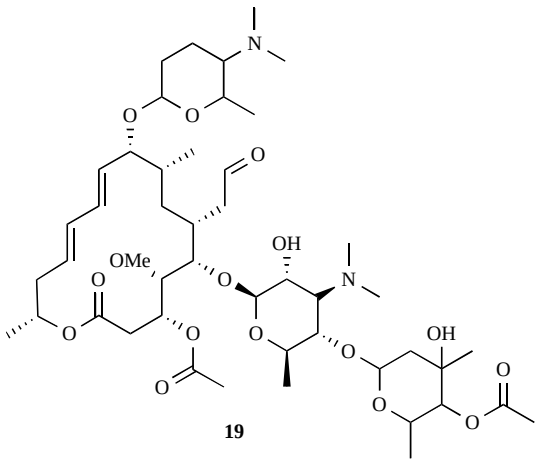

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Fig. (14). 4"-*O*-Acetylspiramycin II (ASPM) (**19**).

Bitespiramycin

Bitespiramycin (Shengjimycin) developed by Chinese Academy of Medical Sciences is a macrolide antibiotic consisting of a mixture of some nine spiramycin ester derivatives [39]. It is a group of 4"-acylated spiramycins and 4"-isovalerylspiramycins as the major components, produced by recombinant *Streptomyces spiramyceticus* F21 harboring a 4"-*O*-acyltransferase gene [40]. It has a similar spectrum of antibiotic activity to spiramycin but has superior pharmacokinetic properties.

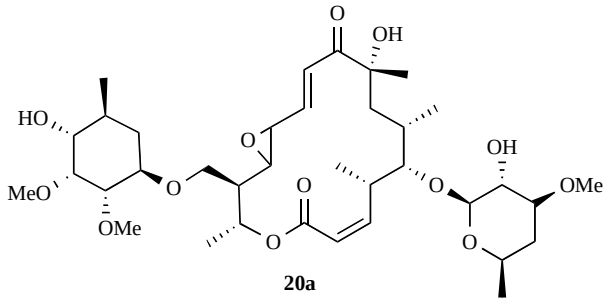
Chalcomycin and its Derivatives

Chalcomycin

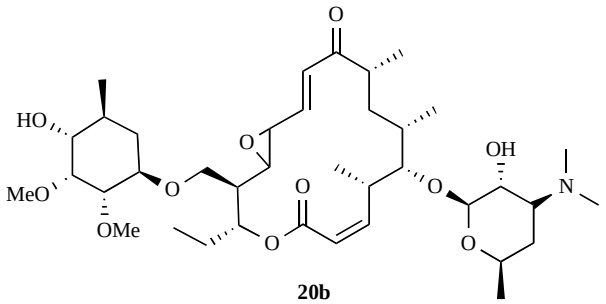
Chalcomycin (**20a**), a 16-membered macrolide antibiotic discovered in the late 1950s in a strain of *Streptomyces bikiniensis*, and mycinamicin I (**20b**) have common features of a 2, 3-trans double bonds in their structures. Chalcomycin contains the 12, 13-epoxide, an 8-hydroxyl group and a neutral sugar D-chalcose in place of the amino sugar at the C-5 position [5]. Chalcomycin do not inhibit the peptidyl transferase reaction due to mycaminose at the C-5 position [10].

250-144C

In 1996, Goot *et al.* [41] reported a new macrolide antibiotic and determined its structure. Antibiotic 250-144C (**21**) was a new chalcomycin type of macrolide antibiotic which is a 16-membered lactone with a new chromophore. It had an unconjugated double bond at C-13 with the ketone group. But the compound showed weak antibacterial activities.

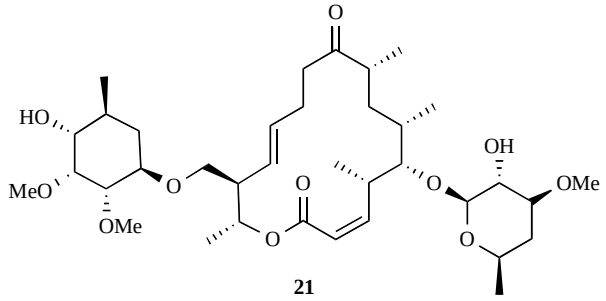


20a



20b

Fig. (15). Chalcomycin (**20a**) and mycinamicin I (**20b**).



21

Fig. (16). 250-144C (**21**).

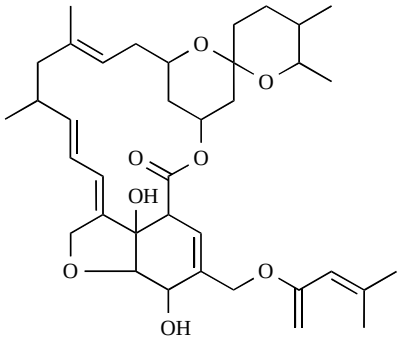
Meilingmycin

China plays a major role in antibiotics production. As we know, apart from producing nanchangmycin, *S. nanchangensis* NS3226 was known to produce another compound, a 16-membered macrolide, meilingmycin (**22**) [42]. It is slightly different from milbemycin α11 and has an aglycone and antiparasitic activity similar to that of avermectin produced by *Streptomyces avermitilis*.

CONCLUSION AND PROSPECT

The 16-membered macrolide derivatives described here are useful for further diverse modifications in the development of new macrolide antibiotics to overcome resistant pathogens. The constant advances occurring in biotechnology have already significantly impacted the study of biosynthesis and genetics involved in macrolide production. This trend allows more directed manipulation of genetic targets to produce new structures. It is very likely

that the macrolide field will remain an interesting and potentially useful area of research for the discovery of new therapeutic agents [43]. Further studies on SARs of 16-membered macrolide derivatives are in progress. The 16-membered macrolides present promising opportunities for the development of new macrolide antibiotics to overcome bacterial resistance.



22

Fig. (17). Meilingmycin (**22**).

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ABBREVIATIONS

MLS = macrolide–lincosamide–streptogramin

RKM = rokitamycin

MOM = miokamycin

MIC = minimal inhibitory concentration

AFB = American foulbrood

SAR = structure-activity relationship

OMT = 5-*O*-mycaminosyltylonolide

CAM = clarithromycin

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