# Chapter 11
# Macrolide Antibiotics

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**Abstract** Macrolide antibiotics are an important class that are used to treat respiratory tract, skin and skin-structure, sexually transmitted, and various other infections. They exert their antimicrobial activity by inhibiting ribosomal protein biosynthesis. Resistance to antibiotics arises when antibiotic binding at its target site is disrupted, efflux pumps remove antibiotic from cells, or antibiotic is converted to an inactive metabolite. Following the isolation of erythromycin and many other macrolides from fermentation broths of soil microbes, three generations of semi-synthetic 14-, 15-, and 16-membered derivatives have been prepared and tested. Two second generation derivatives, clarithromycin and azithromycin, are the more utilized macrolides at this time. Ketolides are third generation derivatives of erythromycin that possess activity against many macrolide-resistant bacteria. Use of the first approved ketolide, telithromycin, has been restricted due to side effects, but some other ketolides have entered into development studies and clinical trials.

## 11.1 Introduction

The development and spread of resistance to antibiotics have been a continual problem since the discovery of antibiotics (Davies and Davies 2010). In the late 1980s, the appearance of resistance to vancomycin in Gram-positive bacteria was especially disturbing (see Chap. 2). This event energized a prolonged search for new agents having activity against resistant bacteria, both Gram-positive and (more recently) Gram-negative species. Many antibiotics (see Chaps. 10, 12–15) inhibit protein synthesis as their mechanism of action (MOA), making it one of the

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most common and important antibacterial mechanisms (Lange et al. 2007). Despite an increasing prevalence of pathogens that show multiple patterns of resistance, this MOA remains as important today as it has been for the past several decades of antibiotic usage. Furthermore, new antimicrobial agents that inhibit some part of protein synthesis continue to be developed.

Macrolide antibiotics are one of the foremost classes that exert their antibacterial activity through this MOA (Hermann 2005; McCoy et al. 2011; Wilson 2004; Yonath 2005). The parent macrolides are produced by fermentation of soil microorganisms and some of these older macrolides are still useful therapeutic agents today (Demain 2009; Demain and Sanchez 2009; Omura 2011). They also represent an invaluable resource of chemical starting materials that have spawned many important semi-synthetic derivatives which possess various improved features responsible for increased efficacy and safety. This chapter will summarize the macrolide antibiotics, both older agents that are still important and newer agents that are in some stage of the preclinical or clinical development pipeline.

## 11.2 Erythromycin and Its Semi-synthetic Derivatives

Macrolide antibiotics constitute a large class that is organized by the size and substitution patterns of their highly substituted macrolactones to which particular saccharide moieties are attached (Kaneko et al. 2007; Kirst 2005; Mitscher 2010). Fermentation-derived macrolide antibiotics have a 14- or 16-membered lactone, while 15-membered macrolides are created by chemical ring expansion of a 14-membered ring. Many other macrolide compounds are known whose macrolactones have different substitution patterns or have fewer than 14 or more than 16 members, but the antibacterial activity of those compounds is generally too weak and/or too limited for useful clinical applications (Shiomi and Ōmura 2002).

Erythromycin A is the prototype of 14-membered macrolide antibiotics (Fig. 11.1). It is the major component of a complex produced by fermentation of a soil actinomycete now classified as *Saccharopolyspora erythraea*. First generation derivatives of erythromycin were synthesized soon after its discovery that included many acid-addition salts, esters, and salt-ester combinations designed to increase stability under acidic conditions (e.g., stomach) and to improve oral bioavailability. Acid-addition salts also improved water solubility for intravenous administration, but intramuscular administration was too painful upon injection to be used. All of these derivatives revert to erythromycin free base, which is the active entity of these first-generation derivatives. Early studies were conducted to learn the cause for the acid instability of erythromycin. These studies discovered a facile intramolecular cyclization by the C-6 hydroxyl group with the C-9 ketone to form a 6,9-hemiketal followed by 8,9-dehydration to initially yield the 8,9-anhydro-6,9-hemiketal intermediate (Fig. 11.1), which then underwent further degradation (Kurath et al. 1971). This insight provided a mechanistic rationale for

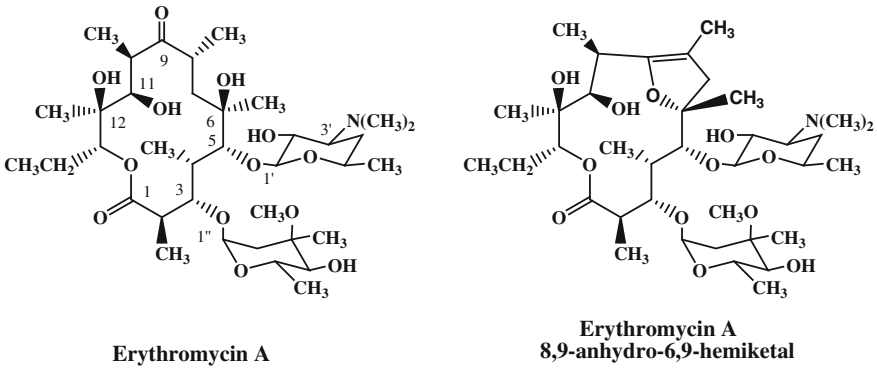



**Fig. 11.1** Structures of erythromycin A and its intramolecular cyclization product

structural modifications of erythromycin that later produced the desired greater stability and oral bioavailability.

Second generation semi-synthetic derivatives of erythromycin were prepared by chemical transformations that modified certain of those functional groups that contribute to the intramolecular cyclization of erythromycin. Early members of this group were erythromycin-11,12-cyclic carbonate, 9-(*S*)-erythromycylamine, and roxithromycin (Fig. 11.2). The presence of either the exocyclic 5-membered ring in the 11,12-cyclic carbonate or the C-9 oxime in roxithromycin made these derivatives less prone than erythromycin to undergo the irreversible intramolecular cyclization sequence. In erythromycylamine, the C-9 ketone was replaced by an amino group which rendered the derivative incapable of forming the 6,9-hemiketal. Erythromycylamine was later re-examined as the active component in the pro-drug, dirithromycin. However, all of these earlier derivatives were superseded by clarithromycin and azithromycin, both of which became the more widely used second generation macrolides (Fig. 11.2) (Sivapalasingam and Steigbigel 2010; Zuckerman et al. 2011).

Clarithromycin is the 6-O-methyl ether of erythromycin, in which the 6-hydroxyl group is substituted and can no longer engage in intramolecular cyclization. Azithromycin is a ring-expanded 15-membered derivative in which the C-9 ketone is replaced via Beckmann rearrangement and N-methylation with a ring-embedded N-methylamino-methylene unit, a change that eliminates the C-9 ketone from participation in intramolecular cyclization. The collective group of compounds having an amino group incorporated within the macrolactone framework has been named azalides. Dirithromycin and flurithromycin were later entries into second generation derivatives (Fig. 11.2). Dirithromycin is an oxazine pro-drug of 9-(*S*)-erythromycylamine. Flurithromycin contains an 8-fluorosubstituent that prevents irreversible dehydration of the 6,9-hemiketal. Each of these diverse modifications provided a unique approach to circumventing the propensity of erythromycin for intramolecular cyclization and thereby achieved greater stability in each individual way.

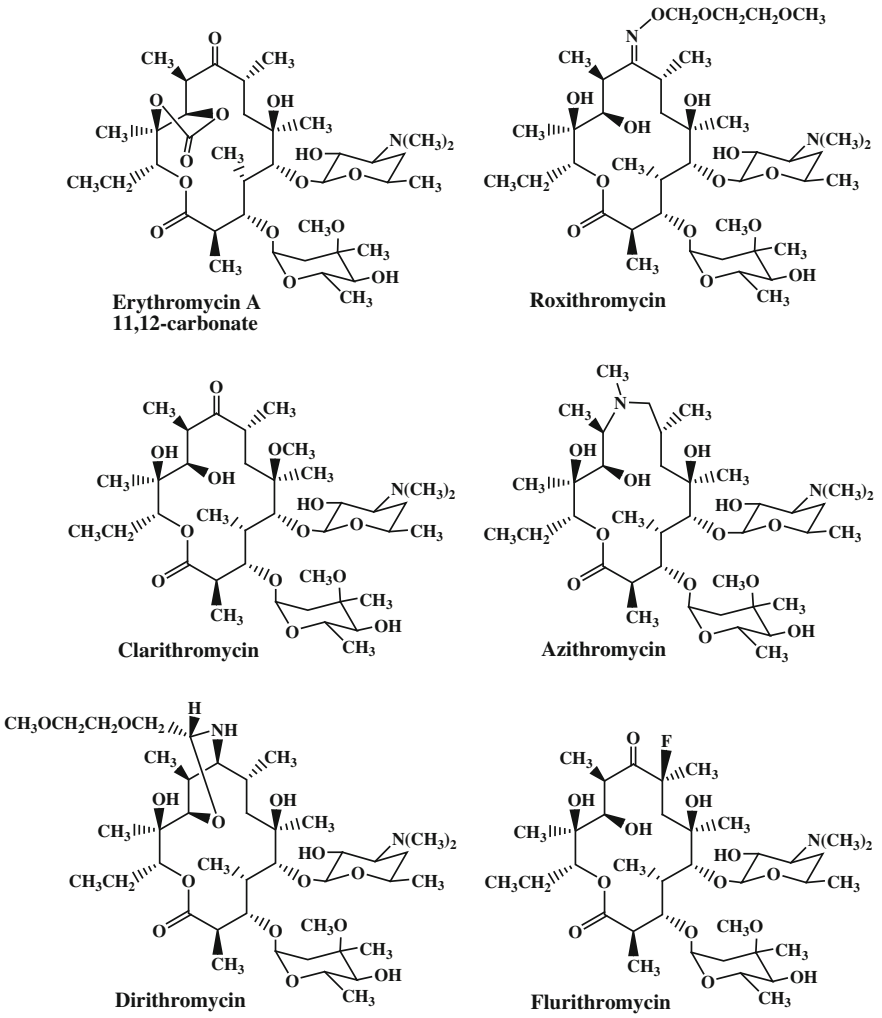



**Fig. 11.2** Structures of second generation derivatives of erythromycin

Ketolides constitute the third generation, so-named due to their 3-keto functionality that replaces the 3-O-cladinosyl moiety of erythromycin, as exemplified by the first commercial ketolide, telithromycin (Ketek®) (Fig. 11.3) (Bryskier and Denis 2002; Sivapalasingam and Steigbigel 2010; Van Bambeke et al. 2008; Zhanel and Neuhauser 2005; Zuckerman et al. 2011). More recent ketolides that have entered the antibiotic pipeline include cethromycin, modithromycin, and solithromycin (Fig. 11.3) (Butler and Cooper 2011; Donadio et al. 2010; Kirst 2010). Cethromycin (Restanza™) originated from the antibiotic discovery programs at Abbott Laboratories (ABT-773) (Hammerschlag and Sharma 2008;

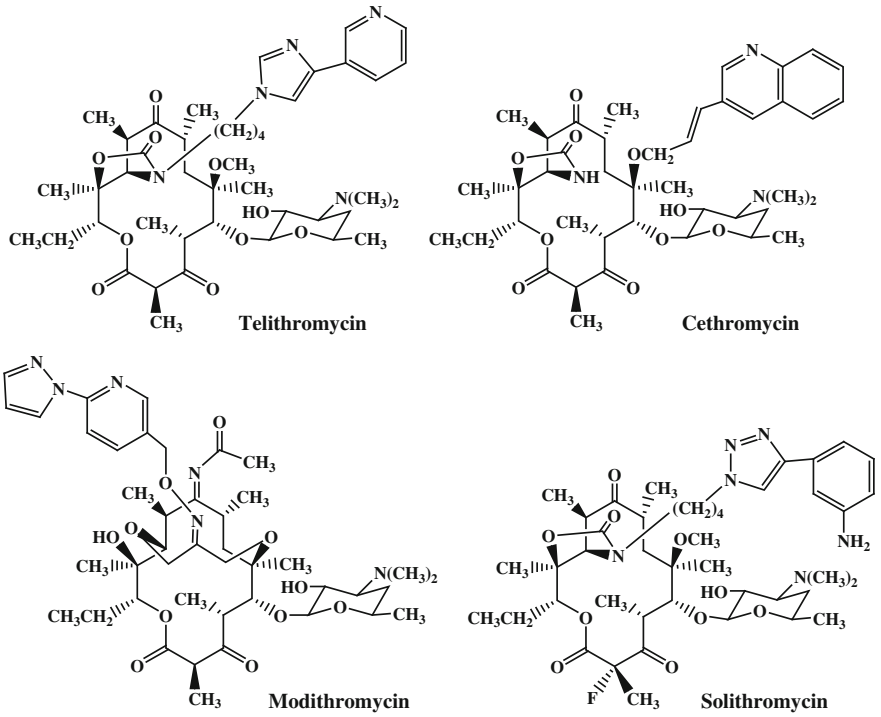



**Fig. 11.3** Structures of representative ketolides

Rafie et al. 2010). It was in late stage development for treating community acquired bacterial pneumonia (CABP) and was also being investigated for biodefense applications. However, its future development is currently uncertain because Advanced Life Sciences suspended operations in May, 2011 (Advanced Life Sciences 2012; Bush and Pucci 2011; Sutcliffe 2011).

Several series of macrolides have been prepared at Enanta Pharmaceuticals that contain additional rings created by different bridging linkages between various hydroxyl groups of erythromycin. These series have thus been given the general names of bicyclolides, tricyclolides, etc. Bicyclolides are being investigated for both oral and intravenous administration against bacterial pathogens in hospital and community settings and are also being tested for biodefense applications against several pathogenic bacteria (Enanta 2012). The initial clinical candidate, modithromycin (formerly EDP-420 and S-013420) (Fig. 11.3), contains an additional internal ring that bridges the C-6 and C-11 hydroxyl groups. It has been jointly investigated in clinical trials with Shionogi & Company (Furuie et al. 2010; Jiang et al. 2009).

Solithromycin (formerly CEM-101) is the first 2-fluoro-ketolide in clinical development. Its structure also has a four-carbon linker between the 11,12-carbamate and a bis-heterocyclic side chain composed of a relatively stable 1,2,3-triazole

and a 2-aminophenyl group (Fig. 11.3) (Pereira and Fernandes 2011). It was licensed by Cempra Pharmaceuticals from Optimer Pharmaceuticals (Cempra 2012). Solithromycin has completed a phase 2 clinical trial for CABP by oral administration while an intravenous formulation is in a phase 1 trial (Cempra 2012; Fernandes et al. 2011; Sutcliffe 2011).

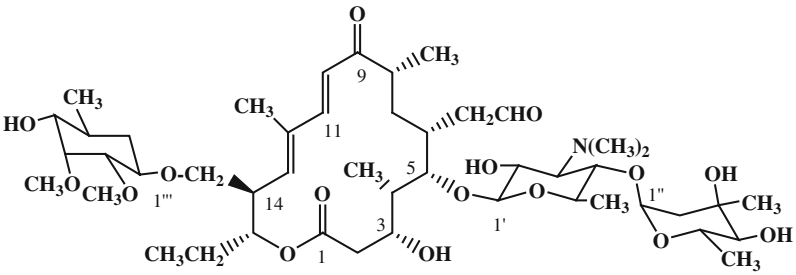
Research is still very actively in progress to discover new derivatives of erythromycin (Kirst 2010; Ma and Ma 2011; Ying and Tang 2010). In addition to new ketolides, other modifications around the 2,3-position of the core macrolactone include the so-called acylides, alkylides and anhydrolides. Several additional modifications are also being investigated around the 11,12-position (Kirst 2010). BAL19403 possesses a heterocyclic substituent linked to a 11,12-lactone rather than a 11,12-cyclic carbamate. It demonstrated good activity against resistant propionibacteria (Heller et al. 2007). Changes in the two saccharide moieties are also being explored with the synthesis of 3′-N- or 4″-O-modified derivatives of erythromycin. These efforts indicate that the search will continue for additional new derivatives of erythromycin having improved clinical efficacy and activity against resistant pathogens.

Macrolide antibiotics also have important applications in veterinary medicine. Two of the more recent azalides, tulathromycin (Draxxin®) and gamithromycin (Zactran®) are used exclusively for veterinary purposes such as treatment of respiratory infections in animals (Forbes et al. 2011; Shryock and Richwine 2010).

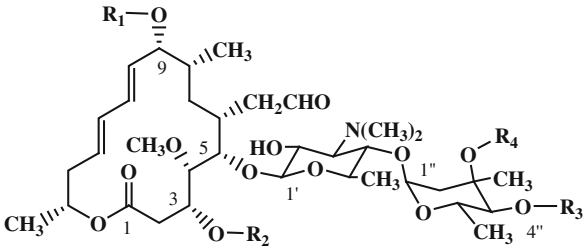
## 11.3 16-Membered macrolide antibiotics

16-Membered macrolide antibiotics are divided into two large families, tylosin and leucomycin-spiramycin, based on different substitution patterns of their macrolactones (Fig. 11.4). Tylosin is produced by fermentation of *Streptomyces fradiae* and is its family prototype. It is an important veterinary antibiotic, but it has not been developed for use in human medicine (Elanco 2012). A few other members of the tylosin family have also been developed exclusively for applications in veterinary medicine, including two semi-synthetic derivatives of tylosin, tilmicosin (Micotil®, Pulmotil®) and tildipirosin (Zuprevo®), which are being used to treat respiratory infections in animals (Buret 2010; Menge et al. 2012). Some clinical investigations have occurred in the past with a few members of the tylosin family, but none of these compounds appear to have yet been successfully developed for human medicine.

The leucomycin family is more numerous and more complicated because many members have been obtained from fermentation of different microorganisms by different research groups and given different names or corporate code numbers (Kirst 2005). Leucomycin was initially isolated as a complex of ten components from culture broths of *Streptomyces kitasatoensis* (Fig. 11.4) (Omura 2011). Midecamycin and spiramycin were also isolated as multi-component complexes from culture broths of *Streptomyces mycarofaciens* and *Streptomyces*



**Tylosin**



**Leucomycin $A_3$ (Josamycin): $R_1$ = $R_4$ = H; $R_2$ = acetyl; $R_3$ = isovaleryl**
**Spiramycin I: $R_1$ = β-D-forosaminyl; $R_2$ = $R_4$ = H; $R_3$ = α-L-mycarosyl**

**Leucomycin $A_5$: $R_1$ = $R_2$ = $R_4$ =H; $R_3$ = *n*-butyryl**
**Rokitamycin: $R_1$ = $R_2$ = H; $R_3$ = *n*-butyryl; $R_4$ = propionyl**

**Midecamycin $A_1$: $R_1$ = $R_4$ = H; $R_2$ = $R_3$ = propionyl**
**Miokamycin: $R_1$ = $R_4$ = acetyl; $R_2$ = $R_3$ = propionyl**

**Fig. 11.4** Structures of representative 16-membered macrolides

*ambofaciens*, respectively. Some members of this family are used in human medicine, such as josamycin (leucomycin $A_3$), midecamycin, and spiramycin. Although none of these 16-membered macrolides have been registered for the U.S. market, spiramycin is used to treat certain infections caused by *Toxoplasma gondii* in pregnant women (Montoya and Remington 2008).

The most important semi-synthetic derivatives in the leucomycin family are miokamycin and rokitamycin (Alvarez-Elcoro and Yao 2002). Chemical acylation of leucomycin-type macrolides, especially of their 3″-hydroxyl group, increased the half-life of antibiotic activity while retaining good in vitro potency. This discovery was applied to prepare the semi-synthetic derivatives miokamycin (9,3″-di-O-acetyl derivative of midecamycin $A_1$) and rokitamycin (3″-O-propionyl derivative of leucomycin $A_5$) (Fig. 11.4). As mentioned above for the 16-membered parent macrolides, neither of these two derivatives has been registered for the U.S. market.

As with the 14-membered family, new research on 16-membered macrolides also continues in the effort to discover new antibiotics (Cui and Ma 2011; Przybylski 2010). However, the amount of effort has been significantly less than that devoted to 14- and 15-membered agents. One reason may be that 16-membered ketolides synthesized thus far have not demonstrated activity comparable to 14-membered ketolides (Creemer et al. 2002; Mutak et al. 2004; Terui et al. 2006). Analogous to 14-membered ketolides, the attachment of additional substituents to the 16-membered ring may be required to achieve the necessary stronger ribosomal binding and greater activity.

## 11.4 Antimicrobial Features

Macrolide antibiotics possess a moderately wide range of antimicrobial activity in which they inhibit susceptible strains of many Gram-positive bacteria, certain Gram-negative bacteria, and a variety of other pathogenic organisms (Dang et al. 2007; Roberts 2008; Sivapalasingam and Steigbigel 2010; Zuckerman et al. 2011). They penetrate well into many cells and tissues and exhibit activity against many microbes that dwell in an intracellular environment (Mulazimoglu et al. 2005). However, they generally lack useful activity against enterococci and most enteric and coliform Gram-negative bacteria. Interestingly, a recent study reported that in vitro activity of macrolides against *Pseudomonas aeruginosa* was highly dependent on the type of growth medium being used for the MIC test. MIC values were much lower when eukaryotic cell growth media were used compared to higher MICs when cation-adjusted Mueller–Hinton broth was employed (Buyck et al. 2011). This MIC differential may further help to explain the positive clinical effects of macrolides that are observed in cases involving *P. aeruginosa*, such as diffuse panbronchiolitis and cystic fibrosis (Crosbie and Woodhead 2009; Friedlander and Albert 2010).

The activity of macrolides may be bactericidal or bacteriostatic, depending on the particular microorganism, antibiotic concentration, contact time, and other experimental conditions. Most macrolides contain an amino group in their structures and thus they are basic substances that form acid-addition salts with increased water solubility. However, the un-ionized free base is the active form, so microbial penetration and antimicrobial activity is increased at higher pH values.

Although second generation macrolides had been more focused toward solving the earlier problems involving stability and oral bioavailability, some of those derivatives also showed greater potency against certain microorganisms that partially expanded the antimicrobial spectrum compared to erythromycin and 16-membered macrolides (Ali et al. 2002; Blondeau et al. 2002; Sivapalasingam and Steigbigel 2010; Zuckerman et al. 2011). Clarithromycin and azithromycin emerged as the more widely used macrolides due to some favorable clinical features, including somewhat broadened spectrum of activity and greater efficacy,

improved pharmacokinetics, less frequent dosing schedule, and better gastrointestinal tolerance. Among some prominent traits of this group, azithromycin was more effective in lowering MIC values against many Gram-negative bacteria while clarithromycin was more active against Gram-positive bacteria. The efficacy of clarithromycin against *Haemophilus influenzae* was aided by its in vivo conversion to its more active 14-hydroxy metabolite whereas azithromycin had a lower MIC against *H. influenzae*. The enhanced activity of these macrolides has been widely useful against pathogens that are responsible for many respiratory tract infections, skin and soft tissue infections, and sexually transmitted diseases. Among other applications, they are used to treat gastrointestinal (GI) problems caused by *Helicobacter pylori*. They exhibit activity against many non-tuberculous mycobacteria, especially against the *Mycobacterium avium* complex (MAC) that has aided treatment of MAC infections in AIDS patients (Young and Bermudez 2002).

With problems of stability and oral bioavailability substantially addressed by several second generation derivatives, the alarming rise in microbial resistance to antibiotics started to draw more attention, especially during the late 1980s. In response to this disturbing development, macrolide research began to shift in order to search for new agents that would combat this dangerous trend. The third generation of macrolides was thus intended to address the growing problems of microbial resistance to antibiotics, resulting in the emergence of the first ketolides in the mid-1990s (Bryskier and Denis 2002; Van Bambeke et al. 2008).

## 11.5 Mechanism of Action

The bacterial ribosome is a large and complex structure composed predominantly of RNA and protein that performs the vital task of bacterial protein biosynthesis. Thus, disruption of ribosome function by antibiotics causes serious deleterious effects to the microorganism, including death. The highly complex nature of protein biosynthesis on the ribosome makes for multiple ways in which the overall process can be disrupted. In addition, a second MOA involving inhibition of ribosome assembly by macrolides has been proposed (Champney 2006; Siibak et al. 2009).

Detailed knowledge has been rapidly expanding about the ribosome's structure, its mechanisms for functioning, and its interactions with antibiotic substances (Allen 2002; Blanchard et al. 2010; Bogdanov et al. 2010; Dunkle et al. 2010; Garrett et al. 2000; Kannan and Mankin 2011; Mankin 2008; McCoy et al. 2011; Wilson 2011). To briefly summarize, the programmed sequential addition of individual amino acids onto a growing peptide chain occurs at the peptidyl transferase center (PTC) located in the large (50S) subunit of the ribosome. The PTC catalyzes the sequential formation of the growing peptide's amide bonds. As the peptide chain becomes extended upon the addition of each new amino acid, the lengthening peptide moves outward through the exit tunnel of the ribosome. Macrolide antibiotics bind in the region of the exit tunnel near the PTC where their

presence either completely blocks or partially hinders progression of the nascent peptide out through this tunnel. Different macrolides may bind in different arrangements, but the overall result is inhibition of protein synthesis by preventing the proper elongation of the peptide. Depending on the macrolide, various types of prematurely terminated peptides may be released. Some macrolides such as 16-membered ones containing the 5-O-mycaminosyl-mycarosyl disaccharide have sufficient length to reach the PTC and disrupt formation of amide bonds.

X-ray crystallographic studies using co-crystals of macrolides bound in the large ribosomal subunit have now been performed using many different macrolides and ribosomes from several different microbes (Wilson 2011). Those results are consistent with the overall MOA and provide valuable visual evidence of how different macrolides bind to particular ribosomes in each individual manner. Although ribosomes are generally considered to have conserved structures, it is now recognized that antibiotic-ribosome interaction and binding may differ between ribosomes from different microbial species, so overly generalized interpretations of results may not be valid (Kannan and Mankin 2011; Wilson 2011). Additional studies are likely forthcoming that will greatly expand our detailed knowledge about this MOA. They will also suggest specific ways by which macrolide binding might be strengthened and thus will guide medicinal chemistry research in synthesizing new more potent derivatives (Sutcliffe 2005; Wimberly 2009). The importance of this technology and its significant impact on new drug discovery was celebrated by the award of the 2009 Nobel Prize in Chemistry to Profs. Ramakrishnan, Steitz, and Yonath for their pioneering work on the structure and function of ribosomes.

## 11.6 Microbial Resistance to Macrolides

The isolation of erythromycin from fermentation cultures and the first reports of clinical studies were both published in 1952 (Haight and Finland 1952; Heilman et al. 1952; McGuire et al. 1952). Unfortunately, microbial resistance to erythromycin was also observed soon after its clinical appearance (Leclercq and Courvalin 1991a). In addition, it was early recognized that the level of resistance could be correlated with the amount of antibiotic usage which had placed selective pressures on the microbial population and thereby selected resistant strains (Westh 1996). The clinical significance of resistance to macrolides was initially considered as low, but as years of antibiotic usage increased, so also did serious concerns steadily increase about the continuous rise in resistance to not just macrolides, but to all antibiotics (Boucher et al. 2009; Leclercq and Courvalin 1991b; Mulazimoglu et al. 2005).

The more common mechanism of resistance to macrolide antibiotics is modification of the target site responsible for activity, which is the ribosome. Other resistance mechanisms include antibiotic efflux systems, decreased uptake or permeability into the cell, various mutations to ribosomal RNA and proteins, and

modification of the antibiotic structure by inactivating enzymes (Dang et al. 2007; Douthwaite and Vester 2000; Mlynarczyk et al. 2010; Roberts 2008; Sutcliffe and Leclercq 2002).

Target site modification in bacteria disrupts macrolide ribosomal binding which thereby prevents or hinders the antibiotic from accomplishing its objective of inhibiting protein synthesis. In one common manifestation, the ribosomal binding sites overlap between the macrolide, lincosaminide, and streptogramin B antibiotics (see Chap. 14) resulting in cross-resistance between these three structurally unrelated classes and producing a phenotype named $MLS_B$ resistance (Leclercq and Courvalin 1991a; Weisblum 1995a). $MLS_B$ resistance is caused by enzymatic $N^6$-methylation of an adenine residue located in the overlapping binding region of ribosomal RNA. That N-methylation produces a conformational change in the ribosome that significantly weakens bonding by the antibiotic. This enzymatic methylation is genetically controlled by numerous readily transferable *erm* (erythromycin ribosome methylase) genes that are now found in a wide host of bacteria (Roberts 2008, 2011). $MLS_B$ resistance can be either inducible or constitutive and 16-membered macrolides are generally non-inducers (Allen 1977, 1995; Weisblum 1995b). Two old fermentation-derived 3-keto-14-membered macrolides (pikromycin and narbomycin) were also shown to be non-inducers that were nevertheless active against macrolide-inducibly-resistant staphylococci (Allen 1977). Ketolides show a similar pattern in their response to inducibility (Bonnefoy et al. 1997). However, like other macrolides, they are not active against constitutively resistant strains (Sivapalasingam and Steigbigel 2010; Van Bambeke et al. 2008).

Ketolides possess several important structural changes compared to traditional derivatives of erythromycin that lead to significant advantages in antimicrobial activity and resistance patterns. These structural changes include replacement of the 3-O-mycarosyl substituent with a 3-keto group, addition of a rigid ring system across either the 11,12- or 6,11-positions, and attachment of a bis-heterocyclic moiety via a short carbon linker to various positions within the C-6 to C-12 region (Fig. 11.3). Among additional changes, modithromycin also contains a C-9 acylimine in place of the C-9 ketone. As a result from these structural changes, ketolides acquired a second ribosomal binding site to accommodate the heterocyclic chain in addition to the single ribosomal binding site used by older macrolides (Dang et al. 2007; Wilson 2011; Zhanel and Neuhauser 2005). X-ray structures of telithromycin-ribosomal complexes depict the binding patterns in these ribosomes (Dunkle et al. 2010; Tu et al. 2005). The second binding site strengthens ketolide-ribosomal binding affinity which increases antimicrobial potency. For macrolide-resistant strains, extension of ketolide binding into a second domain provides a new mechanism to overcome or circumvent the ribosomal N-methylation resistance mechanism and thus gives rise to activity against those resistant bacteria (Zhanel and Neuhauser 2005; Zuckerman et al. 2011).

Analysis of a crystal study of *Escherichia coli* ribosomes complexed with solithromycin proposed the presence of three binding sites with the third site coming from the positioning of the 2-fluoro substituent (Fernandes et al. 2011;

Llano-Sotelo et al. 2010; Sutcliffe 2011). Such a result could further strengthen ketolide-ribosomal binding and increase potency relative to non-fluorinated analogs. However, the exact mechanism and in vitro activity resulting from a 2-fluoro substituent may depend on the specific ketolide structure rather than follow a generalized SAR rule for all ketolides (Hwang et al. 2008; Keyes et al. 2003; Llano-Sotelo et al. 2010). Hydrogen bonding from the 2-aminophenyl group also contributes to overall ribosomal binding of solithromycin. The proposal of three binding sites for a single ketolide structure would provide a valuable new mechanism for overcoming the N-methylation and other macrolide-resistance mechanisms in macrolide resistant strains (McGhee et al. 2010). It will be interesting to watch the results of future SAR studies focused in this direction.

The extended and stronger binding that results from the structural changes in the C-6 to C-12 region of ketolides more than compensates for the reduction in activity that occurs upon removal of the 3-O-cladinosyl subunit from erythromycin, an absence that does have the positive effect of removing inducibility of resistance (Allen 1977). Consequently, ketolides tend to show greater activity compared to erythromycin and second generation derivatives against both susceptible and resistant staphylococci, streptococci, and other important pathogens. 2-Fluoro-ketolides appear to increase that activity differential even further although the universality of that trend is still unproven and needs to be more fully investigated. Another caution is that binding of macrolides to ribosomes from different species may yield different results so over-generalizations should be avoided (Kannan and Mankin 2011; Wilson 2011).

Detailed analyses of comparative potencies or resistance patterns among ketolides and older macrolides are beyond the scope and available space of this review and such surveys have been published by many others (Dang et al. 2007; Rafie et al. 2010; Sivapalasingam and Steigbigel 2010; Sutcliffe 2011; Van Bambeke et al. 2008; Zhanel and Neuhauser 2005; Zuckerman et al. 2011). Driven by the medical needs and therapeutic potential that is still available from the ketolide template, it is likely that the creation of novel ketolide structures has not yet reached any limits and additional innovative structures should be revealed in due course.

## 11.7 Pharmacology

The two semi-synthetic derivatives clarithromycin and azithromycin are the dominant macrolide antibiotics currently being used in clinical practice. They are prescribed to treat upper and lower respiratory tract infections caused by a range of pathogens, skin and skin structure infections, several sexually transmitted diseases, and a wide spectrum of other infections caused by various bacteria and other pathogenic organisms (Van Bambeke et al. 2008; Sivapalasingam and Steigbigel 2010; Zuckerman et al. 2011). Among the latter uses is treatment of MAC infections in AIDS patients and eradication of gastrointestinal *H. pylori* often by

means of combination therapy. Macrolides also play an important clinical role as an alternative to $\beta$-lactam antibiotics for patients who are allergic to the latter agents.

In addition to their overtly bacteriostatic or bactericidal activities against pathogens, macrolides have been long known to display a variety of anti-inflammatory (AIF) and immunomodulatory (IMM) properties in the host that make some significant contributions to the overall efficacy of these agents. Numerous studies, analyses, and reviews of these systems have been made over several decades by many investigators (Altenburg et al. 2011; Buret 2010; Harvey et al. 2009; Kovaleva et al. 2012; Zarogoulidis et al. 2012). However, the complexities of the numerous AIF and IMM networks cause difficulties in separating the component parts and in dissecting primary causes from many secondary effects. The situation is further complicated because different macrolides may show opposite effects, thereby making generalities difficult to establish. Consequently, many of the basic mechanisms by which these effects occur still remain incompletely understood. Some attempts have also been made to create derivatives that dissociate the direct antimicrobial activity from non-antibiotic effects, but this objective has thus far only met with very limited success. The most successful separation of activities has been found with compounds derived from intramolecular cyclization of erythromycin, first as motilin agonists in the GI tract and more recently as lead structures for AIF or IMM applications (Sugawara et al. 2011).

As described above, successive generations of derivatives have steadily improved many clinical attributes of this class, allowing it to remain an important contributor to the therapeutic armamentarium for nearly 60 years. In this therapeutic role, macrolides are generally regarded as among the safest antibiotics, with the majority of side effects involving various disturbances of the GI tract. One advantage of several second generation derivatives was a lower incidence and reduced severity of GI effects compared to erythromycin (Periti et al. 1993).

Telithromycin is the most recent commercial macrolide and is currently the only ketolide that has received regulatory approval, which occurred in Europe and some Latin countries in 2001 and the U.S. in 2004. However, during its more extensive use following the clinical trials and approvals, serious problems were reported which included incidents of severe hepatotoxicity, certain visual side effects, and exacerbation of myasthenia gravis. In response to these safety concerns, stronger labeling warnings were written and in 2007, the U.S. FDA restricted use of telithromycin to the treatment of CABP (Van Bambeke et al. 2008; Sivapalasingam and Steigbigel 2010; Zuckerman et al. 2011). One recent study proposed that certain nicotinic acetylcholine receptors that may be associated with those side effects are located in the liver, eye, and muscle. These receptors may be inhibited by telithromycin and may be responsible for these undesirable effects (Bertrand et al. 2010; Fernandes et al. 2011; Sutcliffe 2011). Furthermore, the pyridine component in telithromycin has been suspected of involvement in this activity. The older macrolides, clarithromycin and azithromycin, and the newer ketolide, solithromycin, did not show the same level of

inhibition as telithromycin, suggesting that this test could perhaps be used to predict the possibility of these side effects. These developments are encouraging that the side effects of telithromycin may be more structure-specific and not shared by all ketolides.

## 11.8 Biosynthesis

Early studies of the biosynthesis of erythromycin and other macrolides revealed the formation of their aglycones by sequential coupling of small organic acids (acetate, propionate, etc.) (Corcoran 1964). Following the addition of each acid, the newly formed subunit was then appropriately modified to give the desired stereospecific sub-structure using the processes of ketone reduction, dehydration, and enoyl reduction as appropriate to produce the final product (Kwan and Schulz 2011). Lastly, cyclization of the resultant 14- or 16-membered acyclic chains yielded the aglycones (Corcoran 1981; Omura and Tanaka 1984).

Later studies discovered a strongly programmed process that assembled the aglycones via large and highly organized modular structures called a polyketide synthase (PKS) (Cortes et al. 1990; Donadio et al. 1991). Following cyclization that cleaves the polyketide chain from the PKS, the resultant aglycone is converted to the macrolide antibiotic by appropriate post-PKS transformations, such as hydroxylation, O-methylation, O-glycosylation, etc. (Rix et al. 2002; Zhao and Liu 2010). Investigations by numerous researchers have revealed many further details about the general biosynthetic pathways and PKS-controlled processes and confirmed the generality of this biosynthetic mechanism for the construction of numerous polyketide structures (Cane 2010; Hertweck 2009; Khosla 2009; McDaniel et al. 2005; van Lanen and Shen 2008). This greatly detailed knowledge about the biochemistry and genetics of biosynthesis now allows more rationale and control for genetic engineering of biosynthetic pathways in microorganisms, including applications for combinatorial biosynthesis to create new molecules and for improvements in the fermentative production of known compounds (Baltz 2006; Khosla et al. 2007). All of these biosynthetic possibilities open additional routes to new structural diversification and nicely complement the chemical synthetic routes to produce new antibiotic structures.

## 11.9 Conclusions

Macrolide antibiotics continue to be an important class for treatment of many infectious diseases. Their 2009 sales in the U.S. were $4.8 billion, making them the fourth largest class in sales (after cephalosporins, broad spectrum penicillins, and fluoroquinolones) (Hamad 2010). Approximately 60 years have passed since erythromycin and many other macrolides were discovered and isolated from

culture broths of soil microorganisms. During that period, an extremely large number of semi-synthetic 14-, 15-, and 16-membered macrolides have been prepared and evaluated, which can be divided conveniently into three generations of derivatives. Two second generation derivatives of erythromycin, clarithromycin and azithromycin, are currently the more utilized macrolides. Ketolides have emerged as third generation derivatives of erythromycin that show useful activity against many macrolide-resistant bacteria. Even though the first approved ketolide, telithromycin, has encountered some serious problems with side effects, other ketolides are being synthesized and some have entered the clinical development pipeline. Based on both the undeveloped potential still remaining for this class and the medical need for new agents, research efforts within the macrolide class will undoubtedly continue. From these continuing efforts, new members possessing important and useful improvements in antimicrobial spectrum, efficacy, and safety should be discovered and developed. Such future discoveries will ensure that the macrolide antibiotic class will remain an important contributor to the global anti-infective armamentarium.

## References

Advanced Life Sciences (2012) http://www.advancedlifesciences.com/phoenix.zhtml?c=190126&p=irol=news&nyo=0

Ali AB, Goldstein FW, Acar JF (2002) In vitro activity of macrolides against traditional susceptible bacteria. In: Schönfeld W, Kirst HA (eds) Macrolide antibiotics. Birkhäuser, Basel

Allen NE (1977) Macrolide resistance in *Staphylococcus aureus*: inducers of macrolide resistance. Antimicrob Agents Chemother 11:669–674

Allen NE (1995) Biochemical mechanisms of resistance to non-cell wall antibacterial agents. Prog Med Chem 32:157–238

Allen NE (2002) Effects of macrolide antibiotics on ribosome function. In: Schönfeld W, Kirst HA (eds) Macrolide antibiotics. Birkhäuser, Basel

Altenburg J, de Graaff CS, van der Werf TS, Boersma WG (2011) Immunomodulatory effects of macrolide antibiotics. Respiration 81:67–87

Alvarez-Elcoro S, Yao JDC (2002) Antimicrobial macrolides in clinical practice. In: Ōmura S (ed) Macrolide antibiotics: chemistry, biology, and practice, 2nd edn. Academic Press, San Diego

Baltz RH (2006) Molecular engineering approaches to peptide, polyketide and other antibiotics. Nat Biotech 24:1533–1540

Bertrand D, Bertrand S, Neveu E, Fernandes P (2010) Molecular characterization of off-target activities of telithromycin: a potential role for nicotinic acetylcholine receptors. Antimicrob Agents Chemother 54:5399–5402

Blanchard SC, Cooperman BS, Wilson DN (2010) Probing translation with small-molecule inhibitors. Chem Biol 17:633–645

Blondeau JM, DeCarolis E, Metzler KL, Hansen GT (2002) The macrolides. Expert Opin Investig Drugs 11:189–215

Bogdanov AA, Sumbatyan NV, Shishkina AV, Karpenko VV, Korshunova GA (2010) Ribosomal tunnel and translation regulation. Biochem (Moscow) 75:1501–1516

Bonnefoy A, Girard AM, Agouridas C, Chantot JF (1997) Ketolides lack inducibility properties of $MLS_B$ resistance phenotype. J Antimicrob Chemother 40:85–90

Boucher HW, Talbot GH, Bradley JS et al (2009) Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Inf Dis 48:1–12
Bryskier A, Denis A (2002) Ketolides: novel antibacterial agents designed to overcome resistance to erythromycin A within gram-positive cocci. In: Schönfeld W, Kirst HA (eds) Macrolide antibiotics. Birkhäuser, Basel
Buret AG (2010) Immuno-modulation and anti-inflammatory benefits of antibiotics: the example of tilmicosin. Can J Vet Res 74:1–10
Bush K, Pucci MJ (2011) New antimicrobial agents on the horizon. Biochem Pharmacol 82:1528–1539
Butler MS, Cooper MA (2011) Antibiotics in the clinical pipeline. J Antibiot 64:413–425
Buyck J, Tulkens PM, Van Bambeke F (2011) Increased susceptibility of *Pseudomonas aeruginosa* to macrolides in biologically-relevant media by modulation of outer membrane permeability and of efflux pump expression. 51st Interscience conference on antimicrobial agents and chemotherapy, Chicago, 17–20 Sep, IL; E-122
Cempra Pharmaceuticals (2012) http://www.cempra.com
Cane DE (2010) Programming of erythromycin biosynthesis by a modular polyketide synthase. J Biol Chem 285:27517–27523
Champney WS (2006) The other target for ribosomal antibiotics: inhibition of bacterial ribosomal subunit formation. Infect Disorders-Drug Targets 6:377–390
Corcoran JW (1964) The biosynthesis of erythromycin. Lloydia 27:1–14
Corcoran JW (1981) Biochemical mechanisms in the biosynthesis of the erythromycins. In: Corcoran JW (ed) Antibiotics, vol 4: Biosynthesis. Springer, Berlin
Cortes J, Haydock SF, Roberts GA, Bevitt DJ, Leadlay PF (1990) An unusually large multifunctional polypeptide in the erythromycin-producing polyketide synthase of *Saccharopolyspora erythraea*. Nature 348:176–178
Creemer LC, Toth JE, Kirst HA (2002) Synthesis and in vitro antimicrobial activity of 3-keto 16-membered macrolides derived from tylosin. J Antibiot 55:427–436
Crosbie PA, Woodhead MA (2009) Long-term macrolide therapy in chronic inflammatory airway diseases. Eur Respir J 33:171–181
Cui W, Ma S (2011) Recent advances in the field of 16-membered macrolide antibiotics. Mini-Rev Med Chem 11:1009–1018
Dang V, Nanda N, Cooper TW, Greenfield RA, Bronze MS (2007) Macrolides, azalides, ketolides, lincoamides, and streptogramins. J Okla State Med Assoc 100:75–81
Davies J, Davies D (2010) Origins and evolution of antibiotic resistance. Microbiol Mol Biol Rev 74:417–433
Demain AL (2009) Antibiotics: natural products essential to human health. Med Res Rev 29:821–842
Demain AL, Sanchez S (2009) Microbial drug discovery: 80 years of progress. J Antibiot 62:5–16
Donadio S, Staver MJ, McAlpine JB, Swanson SJ, Katz L (1991) Modular organization of genes required for complex polyketide biosynthesis. Science 252:675–679
Donadio S, Maffioli S, Monciardini P, Sosio M, Jabes D (2010) Antibiotic discovery in the twenty-first century: current trends and future perspectives. J Antibiot 63:423–430
Douthwaite S, Vester B (2000) Macrolide resistance conferred by alterations in the ribosome target site. In: Garrett RA, Douthwaite SR, Liljas A, Matheson AT, Moore PB, Noller HF (eds) The ribosome: structure, function, antibiotics, and cellular interactions. ASM Press, Washington, DC
Dunkle JA, Xiong L, Mankin AS, Cate JHD (2010) Structures of the *Escherichia coli* ribosome with antibiotics bound near the peptidyl transferase center explain spectra of drug action. Proc Natl Acad Sci U S A 107:17152–17157
Elanco Animal Health (2012) http://www.elanco.com.au/product_range/index.html
Enanta Pharmaceuticals (2012) http://www.enanta.com
Fernandes P, Pereira D, Jamieson B, Keedy K (2011) Solithromycin. Drugs Future 36:751–758

Forbes AB, Ramage C, Sales J, Baggott D, Donachie W (2011) Determination of the duration of antibacterial efficacy following administration of gamithromycin using a bovine *Mannheimia haemolytica* challenge model. Antimicrob Agents Chemother 55:831–835

Friedlander AL, Albert RK (2010) Chronic macrolide therapy in inflammatory airways diseases. Chest 138:1202–1212

Furuie H, Saisho Y, Yoshikawa T, Shimada J (2010) Intrapulmonary pharmacokinetics of S-013420, a novel bicyclolide antibacterial, in healthy Japanese subjects. Antimicrob Agents Chemother 54:866–870

Garrett RA, Douthwaite SR, Liljas A, Matheson AT, Moore PB, Noller HF (eds) (2000) The ribosome: structure, function, antibiotics, and cellular interactions. ASM Press, Washington, DC

Haight TH, Finland M (1952) Laboratory and clinical studies on erythromycin. N Eng J Med 247:227–232

Hamad B (2010) The antibiotics market. Nat Rev Drug Discov 9:675–676

Hammerschlag MR, Sharma R (2008) Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. Expert Opin Investig Drugs 17:387–400

Harvey RJ, Wallwork BD, Lund VJ (2009) Anti-inflammatory effects of macrolides: applications in chronic rhinosinusitis. Immunol Allergy Clin N Am 29:689–703

Heilman FR, Herrell WE, Wellman WE, Geraci JE (1952) Some laboratory and clinical observations on a new antibiotic, erythromycin (ilotycin). Proc Staff Meet Mayo Clin 27:285–304

Heller S, Kellenberger L, Shapiro S (2007) Antipropionibacterial activity of BAL19403, a novel macrolide antibiotic. Antimicrob Agents Chemother 51:1956–1961

Hermann T (2005) Drugs targeting the ribosome. Curr Opin Struct Biol 15:355–366

Hertweck C (2009) The biosynthetic logic of polyketide diversity. Angew Chem Int Ed 48:4688–4716

Hwang C-K, Duffield J, Chiu Y-H, Liang C-H, Yao S, Roberets N, Babakhani F, Sears P, Shue Y-K, Ichikawa Y, Fernandes P, Pereira D, Romero A (2008) SAR of 11,12-carbamate macrolides/ketolides linked with 1,4-substituted-[1,2,3]-triazoles. 48th Interscience conference on antimicrobial agents and chemotherapy, Washington, 25–28 Oct, DC; F1-3973

Jiang L, Wang M, Or YS (2009) Pharmacokinetics of EDP-420 after ascending single oral doses in healthy adult volunteers. Antimicrob Agents Chemother 53:1786–1792

Kaneko T, Dougherty TJ, Magee TV (2007) Macrolide antibiotics. In: Triggle DJ, Taylor JB (eds) Comprehensive medicinal chemistry II, vol 7. Elsevier, Oxford

Kannan K, Mankin AS (2011) Macrolide antibiotics in the ribosome exit tunnel: species-specific binding and action. Ann N Y Acad Sci 1241:33–47

Keyes RF, Carter JJ, Englund EE, Daly MM, Stone GG, Nilius AM, Ma Z (2003) Synthesis and antibacterial activity of 6-O-arylbutynyl ketolides with improved activity against some key erythromycin-resistant pathogens. J Med Chem 46: 1795–1798

Khosla C (2009) Structures and mechanisms of polyketide synthases. J Org Chem 74:6416–6420

Khosla C, Tang Y, Chen AY, Schnarr NA, Cane DE (2007) Structure and mechanism of the 6-deoxyerythronolide B synthase. Annu Rev Biochem 76:195–221

Kirst HA (2005) Macrolide antibiotics. In: Seidel A (ed) Kirk-Othmer encyclopedia of chemical technology, 5th edn. Wiley, New York

Kirst HA (2010) New macrolide, lincosaminide and streptogramin B antibiotics. Expert Opin Ther Patents 20:1343–1357

Kovaleva A, Remmelts HH, Rijkers GT, Hoepelman AI, Biesma DH, Oosterheert JJ (2012) Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. J Antimicrob Chemother 67:530–540

Kurath P, Jones PH, Egan RS, Perun TJ (1971) Acid degradation of erythromycin A and erythromycin B. Experientia 27:362

Kwan DH, Schulz F (2011) The stereochemistry of complex polyketide biosynthesis by modular polyketide synthases. Molecules 16:6092–6115

Lange RP, Locher HH, Wyss PC, Then RL (2007) The targets of currently used antibacterial agents: lessons for drug discovery. Curr Pharm Design 13:3140–3154
Leclercq R, Courvalin P (1991a) Bacterial resistance to macrolide, lincosamide, and streptogramin antibiotics by target modification. Antimicrob Agents Chemother 35:1267–1272
Leclercq R, Courvalin P (1991b) Intrinsic and unusual resistance to macrolide, lincosamide, and streptogramin antibiotics in bacteria. Antimicrob Agents Chemother 35:1273–1276
Llano-Sotelo B, Dunkle J, Klepacki D, Zhang W, Fernandes P, Cate JHD, Mankin AS (2010) Binding and action of CEM-101, a new fluoroketolide antibiotic that inhibits protein synthesis. Antimicrob Agents Chemother 54:4961–4970
Ma X, Ma S (2011) Significant breakthroughs in search for anti-infectious agents derived from erythromycin A. Curr Med Chem 18:1993–2015
Mankin AS (2008) Macrolide myths. Curr Opin Microbiol 11:414–421
McCoy LS, Xie Y, Tor Y (2011) Antibiotics that target protein synthesis. WIREs RNA 2:209–232
McDaniel R, Welch M, Hutchinson CR (2005) Genetic approaches to polyketide antibiotics. Chem Rev 105:543–558
McGhee P, Clark C, Kosowska-Shick KM, Nagai K, Dewasse B, Beachel L, Appelbaum PC (2010) *In vitro* activity of CEM-101 against *Streptococcus pneumoniae* and *Streptococcus pyogenes* with defined macrolide resistance mechanisms. Antimicrob Agents Chemother 54:230–238
McGuire JM, Bunch RL, Anderson RC, Boaz HE, Flynn EH, Powell HM, Smith JW (1952) Ilotycin, a new antibiotic. Antibiot Chemother 2:281–283
Menge M, Rose M, Bohland C, Zschiesche E, Kilp S, Metz W, Allan M, Ropke R, Nurnberger M (2012) Pharmacokinetics of tildipirosin in bovine plasma, lung tissue, and bronchial fluid (from live, nonanesthetized cattle). J Vet Pharmacol Ther 35:550–559
Mitscher LA (2010) Tetracycline, aminoglycoside, macrolide, and miscellaneous antibiotics. In: Abraham DJ, Rotella DP (eds) Burger's medicinal chemistry, drug discovery, and development, 7th edn. Wiley, New York
Mlynarczyk B, Mlynarczyk A, Kmera-Muszynska, Majewski S, Mlynarczyk G (2010) Mechanisms of resistance to antimicrobial drugs in pathogenic Gram-positive cocci. Mini-Rev Med Chem 10:928–937
Montoya JG, Remington JS (2008) Management of *Toxoplasma gondii* infection during pregnancy. Clin Infect Dis 47:554–566
Mulazimoglu L, Tulkens PM, Van Bambeke F (2005) Macrolides. In: Yu VL, Edwards G, McKinnon PS, Peloquin C, Morse GD (eds) Antimicrobial therapy and vaccines, vol 2. E-Sun Technologies, Pittsburgh
Mutak S, Marsic N, Kramaric MD, Pavlovic D (2004) Semisynthetic macrolide antibacterials derived from tylosin. Synthesis and structure-activity relationships of novel desmycosin analogues. J Med Chem 47:411–431
Omura S (2011) Microbial metabolites: 45 years of wandering, wondering and discovering. Tetrahedron 67:6420–6459
Omura S, Tanaka Y (1984) Biochemistry, regulation, and genetics of macrolide production. In: Ōmura S (ed) Macrolide antibiotics: chemistry, biology, and practice, 1st edn. Academic Press, Orlando
Pereira D, Fernandes P (2011) Synthesis and antibacterial activity of novel 4-aryl-[1,2,3]-triazole containing macrolides. Bioorg Med Chem Lett 21:510–513
Periti P, Mazzei T, Mini E, Novelli A (1993) Adverse effects of macrolide antibacterials. Drug Saf 9:346–364
Przybylski P (2010) Modifications and biological activity of natural and semisynthetic 16-membered macrolide antibiotics. Curr Med Chem 18:1993–2015
Rafie S, MacDougall C, James CL (2010) Cethromycin: a promising new ketolide antibiotic for respiratory infections. Pharmacother 30:290–303
Rix U, Fischer C, Remsing LL, Rohr J (2002) Modification of post-PKS tailoring steps through combinatorial biosynthesis. Nat Prod Rep 19:542–580

Roberts MC (2008) Update on macrolide-lincosamide-streptogramin, ketolide, and oxazolidinone resistance genes. FEMS Microbiol Lett 282:147–159
Roberts MC (2011) Environmental macrolide-lincosamide-streptogramin and tetracycline resistant bacteria. Frontiers Microbiol 2:40
Shiomi K, Ōmura S (2002) Discovery of new macrolides. In: Ōmura S (ed) Macrolide antibiotics: chemistry, biology, and practice, 2nd edn. Academic Press, San Diego
Shryock TR, Richwine A (2010) The interface between veterinary and human antibiotic use. Ann N Y Acad Sci 1213:92–105
Siibak T, Peil L, Xiong L, Mankin A, Remme J, Tenson T (2009) Erythromycin- and chloramphenicol-induced ribosomal assembly defects are secondary effects of protein synthesis inhibition. Antimicrob Agents Chemother 53:563–571
Sivapalasingam S, Steigbigel NH (2010) Macrolides, clindamycin, and ketolides. In: Mandell GL, Bennett JE, Dolin R (eds) Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th edn. Churchill Livingstone, Philadelphia
Sugawara A, Sueki A, Hirose T, Nagai K, Gouda H, Shima H, Akagawa KS, Omura S, Sunazuka T (2011) Novel 12-membered non-antibiotic macrolides from erythromycin A: EM900 series as novel leads for anti-inflammatory and/or immunomodulatory agents. Bioorg Med Chem Lett 21:3373–3376
Sutcliffe JA (2005) Improving on nature: antibiotics that target the ribosome. Curr Opin Microbiol 8:534–542
Sutcliffe JA (2011) Antibiotics in development targeting protein synthesis. Ann N Y Acad Sci 1241:122–152
Sutcliffe JA, Leclercq R (2002) Mechanisms of resistance to macrolides, lincosamides, and ketolides. In: Schönfeld W, Kirst HA (eds) Macrolide antibiotics. Birkhäuser, Basel
Terui Y, Kinoshita K, Kaneda Y, Akashi T, Hamaguchi T, Kawashima A (2006) Synthesis of 2-methyl 16-membered macrolide derived from tylosin. J Antibiot 59:98–104
Tu D, Blaha G, Moore PB, Steitz TA (2005) Structures of $MLS_BK$ antibiotics bound to mutated large ribosomal subunits provide a structural explanation for resistance. Cell 121:257–270
Van Bambeke F, Harms JM, Van Laethem Y, Tulkens PM (2008) Ketolides: pharmacological profile and rational positioning in the treatment of respiratory tract infections. Expert Opin Pharmacother 9:267–283
Van Lanen SG, Shen B (2008) Advances in polyketide synthase structure and function. Curr Opin Drug Discov Devel 11:186–195
Weisblum B (1995a) Erythromycin resistance by ribosome modification. Antimicrob Agents Chemother 39:577–585
Weisblum B (1995b) Insights into erythromycin action from studies of its activity as inducer of resistance. Antimicrob Agents Chemother 39:797–805
Westh H (1996) Erythromycin-resistant *Staphylococcus aureus* in Denmark. APMIS Supplement 57:1–37
Wilson DN (2004) Antibiotics and the inhibition of ribosome function. In: Nierhaus KH, Wilson DN (eds) Protein synthesis and ribosome function. Wiley-VCH, Weinheim
Wilson DN (2011) On the specificity of antibiotics targeting the large ribosomal subunit. Ann N Y Acad Sci 1241:1–16
Wimberly BT (2009) The use of ribosomal crystal structures in antibiotic drug design. Curr Opin Investig Drugs 10:750–765
Ying L, Tang D (2010) Recent advances in the medicinal chemistry of novel erythromycin-derivatized antibiotics. Curr Topics Med Chem 10:1441–1469
Yonath A (2005) Antibiotics targeting ribosomes: resistance, selectivity, synergism, and cellular regulation. Annu Rev Biochem 74:649–679
Young LS, Bermudez LE (2002) Activity of macrolides against mycobacteria. In: Schönfeld W, Kirst HA (eds) Macrolide antibiotics. Birkhäuser, Basel
Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K (2012) Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. Eur J Clin Pharmacol 68:479–503

Zhanel GG, Neuhauser MM (2005) Ketolides (telithromycin, cethromycin). In: Yu VL, Edwards G, McKinnon PS, Peloquin C, Morse GD (eds) Antimicrobial therapy and vaccines, vol 2. E-Sun Technologies, Pittsburgh

Zhao L, Liu H-W (2010) Pathway and enzyme engineering and applications for glycodiversification. In: Yeh W-K, Yang H-C, McCarthy JR (eds) Enzyme technologies: Metagenomics, evolution, biocatalysis, and biosynthesis. Wiley, Hoboken

Zuckerman JM, Qamar F, Bono BR (2011) Review of macrolides (azithromycin, clarithromycin), ketolides (telithromycin) and glycylcyclines (tigecycline). Med Clin N Am 95:761–791