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A Chemist's Survey of Different Antibiotic Classes

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1.1

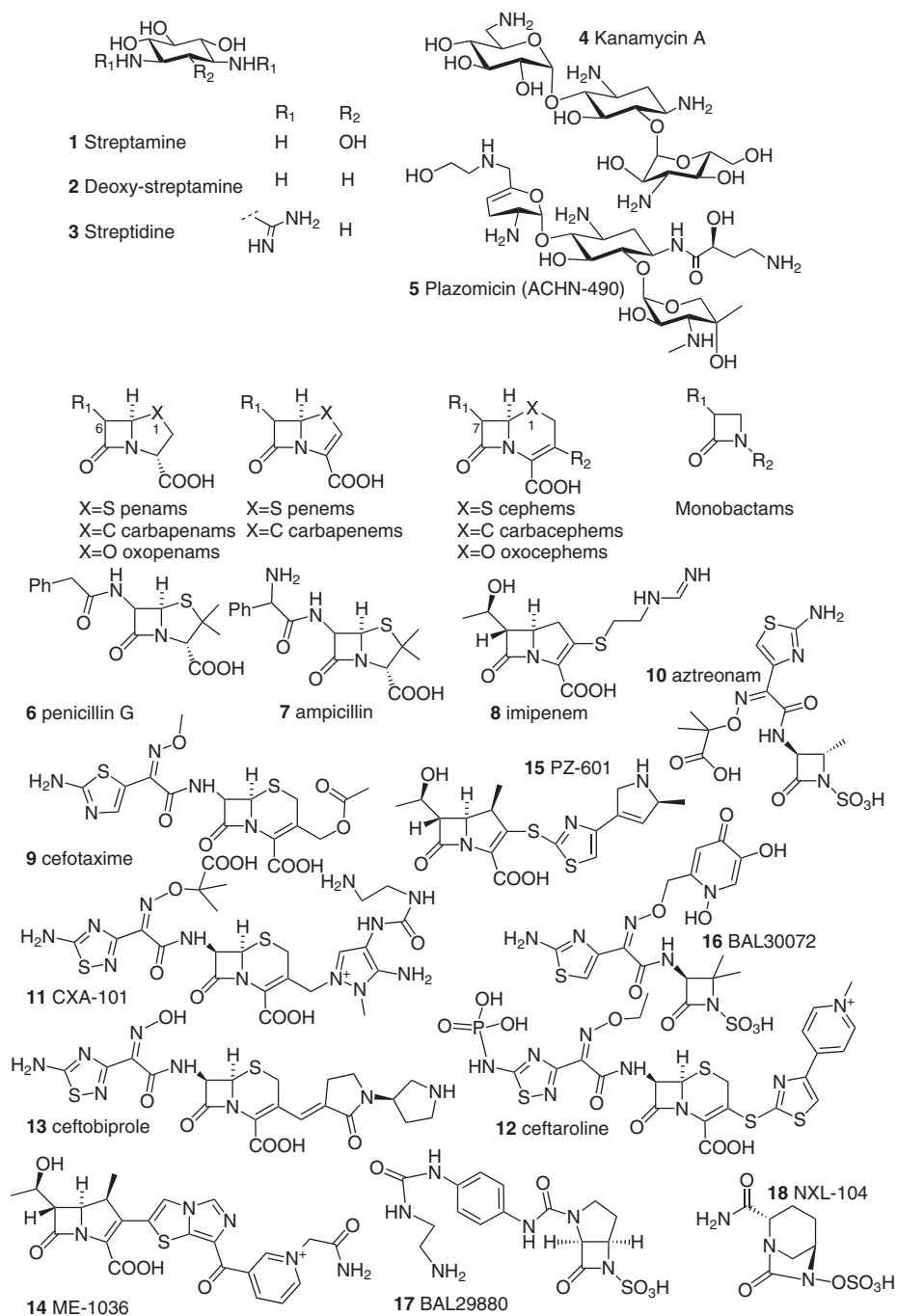
Introduction

More than 20 novel classes of antibiotics were produced between 1930 and 1962. Since then, only four new classes of antibiotics were marketed. Interestingly, none of these new classes is really novel: daptomycin, approved in 2000, was discovered in the early 1980s; linezolid, approved in 2000, derives from a synthetic lead discovered in the 1970s; pleuromutilins, approved in 2007, have been widely used for about 30 years in veterinary medicine; fidaxomicin, approved in 2011, was first reported in the 1970s. This chapter reviews the main classes of antibiotics in clinical use organized by their chemical structure. For each class, the natural or synthetic origin and a description of the chemical structure are presented. The mechanism of action and spectrum of activity are only briefly indicated as they are discussed more deeply in the subsequent chapters. A short summary of the early structure–activity relationships (SARs) leading to the most known derivatives is described followed by a short overview of the most recent analogous currently under clinical development [1–3].

1.2

Aminoglycosides

Aminoglycosides (Figure 1.1) were first established as antibiotics in the 1940s and are still widely used worldwide. They are obtained by fermentation of *Streptomyces*, *Micromonospora*, and *Bacillus*; irreversibly inhibit protein synthesis by acting on the ribosome; and are especially active against gram-negative bacteria. They chemically consist of an aminocyclitol substituted with amino sugars. A classification proposed by Umezawa was based on the central structure, which can be streptamine **1**, 2-deoxystreptamine **2**, or streptidine **3**. A relevant number of natural and semisynthetic derivatives have been obtained since their discovery with the aim of bettering the toxicity issues linked to these structures, mainly oto- and nephrotoxicity, and to fight the increased resistance that mostly arises from structural modification of the

Figure 1.1 Aminoglycosides and β -lactam antibiotics.

aminoglycosides by specific enzymes expressed by resistant strains. These studies highlighted the importance of the number and position of the amino groups for the antibacterial activity. For example, the derivatization of the amino and alcoholic groups in kanamycin **4** resulted in an increased potency together with a reduced susceptibility to the inactivating enzymes that act by acetylation of 2'- and 6'-position and by phosphorylation on position 3'. Recently, interest in this class increased again owing to their spectrum of activity and the observed synergistic activity with other antibiotic classes [1]. Among the recent derivatives, plazomicin (ACHN-490) **5**, a semisynthetic derivative of sisomicin, shows significant improved activity against amikacin- and/or gentamicin-resistant strains and is currently under phase II clinical study [2, 3].

1.3

β -Lactams

β -Lactam antibiotics, discovered in the 1930s and produced by the fungus *Penicillium*, are a wide class of antibiotics, characterized by the presence of an azetidinone nucleus containing the carbonyl β -lactam, essential for the activity. Different subclasses of β -lactams can be defined depending on the chemical substitutions of the central β -lactamic core (Figure 1.1). The azetidinone can be fused with a saturated or unsaturated pentacycle or hexacycle and position 1 of this ring can be occupied by a sulfur, oxygen, or carbon atom. Thus, penicillins, including penams, carbapenams, and oxopenams, contain a saturated pentacycle (see penicillin B **6** and ampicillin **7**), penems, and carbapenems contain an unsaturated pentacycle (imipenem **8**) and cephalosporins, including cepheems, carbacephems, and oxacephems, contain an unsaturated hexacycle (cefotaxime **9**). Finally, the azetidinone can be alone and not fused with another ring originating monolactams or monobactams (aztreonam **10**). All β -lactams act on cell-wall biosynthesis, targeting the penicillin-binding protein (PBP) enzymes involved in the biosynthesis of the peptidoglycan. In the many decades after penicillin discovery in the 1930s, a huge number of natural, synthetic, and semisynthetic β -lactams were discovered and produced [4]. Initially, position 6 of penicillin was extensively modified to increase the stability of the β -lactam and to overcome the resistance mostly mediated by the production of a PBP with reduced affinity for β -lactams. In cephalosporins, a similar approach by modification of the side chain in position 7 gave rise to new generations of semisynthetic cephalosporins. Initially active mainly on gram-positive bacteria, newer generations have significantly greater gram-negative antimicrobial properties. In the next generations, the *N*-acyl side chain was then coupled with structurally complex heterocycles at position C-3 containing a positive charge at their terminus (Figure 1.1) [5]. The resulting cephalosporins CXA-101 **11**, ceftaroline **12**, and ceftobiprole **13** have exceptional gram-positive activity that also crosses over to some gram negatives [6]. The same type of positively charged heterocycle was also incorporated in position C-2 of the carbapenems (ME-1036 **14**). The injectable carbapenem PZ-601 **15** has shown potent activity against drug-resistant gram-positive

pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and is currently undergoing phase II studies. Among monobactams, in which aztreonam is the only representative widely used in clinics, the newest generation incorporates a siderophore substructure to facilitate bacterial uptake (BAL-30072 **16**). Finally, combinations of a β -lactam with a β -lactamase inhibitor have been successfully used to achieve antibacterial efficacy without accelerating resistance development. Clavulanic acid was the first β -lactamase inhibitor used in combination drugs followed by sulbactam and tazobactam, and more recently BAL29880 **17**, all possessing a β -lactam chemical structure [5]. Recently, a novel bicyclic, non- β -lactam β -lactamase inhibitor (NXL104 **18**) is under clinical evaluation [7].

1.4

Linear Peptides

In this family, gramicidins, dalbaheptides, and lantibiotics are grouped. In all these molecules, the main peptidic chains remain linear and no cyclization occurs at the N- or C-terminal amino acid, yet rings can be present because of cyclization between side chains belonging to different residues. Gramicidin D is a heterogeneous mixture of six strictly related compounds, gramicidins A, B, and C obtained from *Bacillus brevis* and collectively called *gramicidin D* [8]. In contrast to gramicidin S, which is a cyclic peptide, gramicidin D contains linear pentadecapeptides with alternating L- and D-amino acids, sharing the general formula: formyl-L-X-Gly-L-Ala-D-Leu-L-Ala-D-Val-L-Val-D-Val-L-Trp-D-Leu-L-Y-D-Leu-L-Trp-D-Leu-L-Trp-ethanolamine, where amino acids X and Y depend on the gramicidin molecule. X can be Val and iLeu, while Y represents an aromatic amino acid among which are Trp, Phe, and Tyr. The alternating stereochemical configuration (in the form of D and L) of the amino acids is crucial for antibiotic activity. In membranes, gramicidin adopts a β -helix three-dimensional conformation forming channels that are specific to monovalent cations, thus increasing the permeability of the bacterial cell membrane and thereby destroying the ion gradient between the cytoplasm and the extracellular environment.

1.4.1

Glycopeptides-Dalbaheptides

Dalbaheptides (Figure 1.2) are composed of seven amino acids cross-linked to generate a rigid concave shape. This configuration forms the basis of their particular mechanism of action that involves the complexation with the D-alanyl-D-alanine terminus of bacterial cell-wall components. As this mechanism of action is the distinguishing feature of these glycopeptides, the term *dalbaheptide*, from D-al(anyl-D-alanine)b(inding)a(ntibiotics) having hept(apept)ide structure, has been proposed to distinguish them within the larger and diverse groups of glycopeptide antibiotics [9]. Five of the seven amino acids forming the peptidic skeleton are common to all dalbaheptides. Vancomycin **19**, the first dalbaheptide introduced into clinical

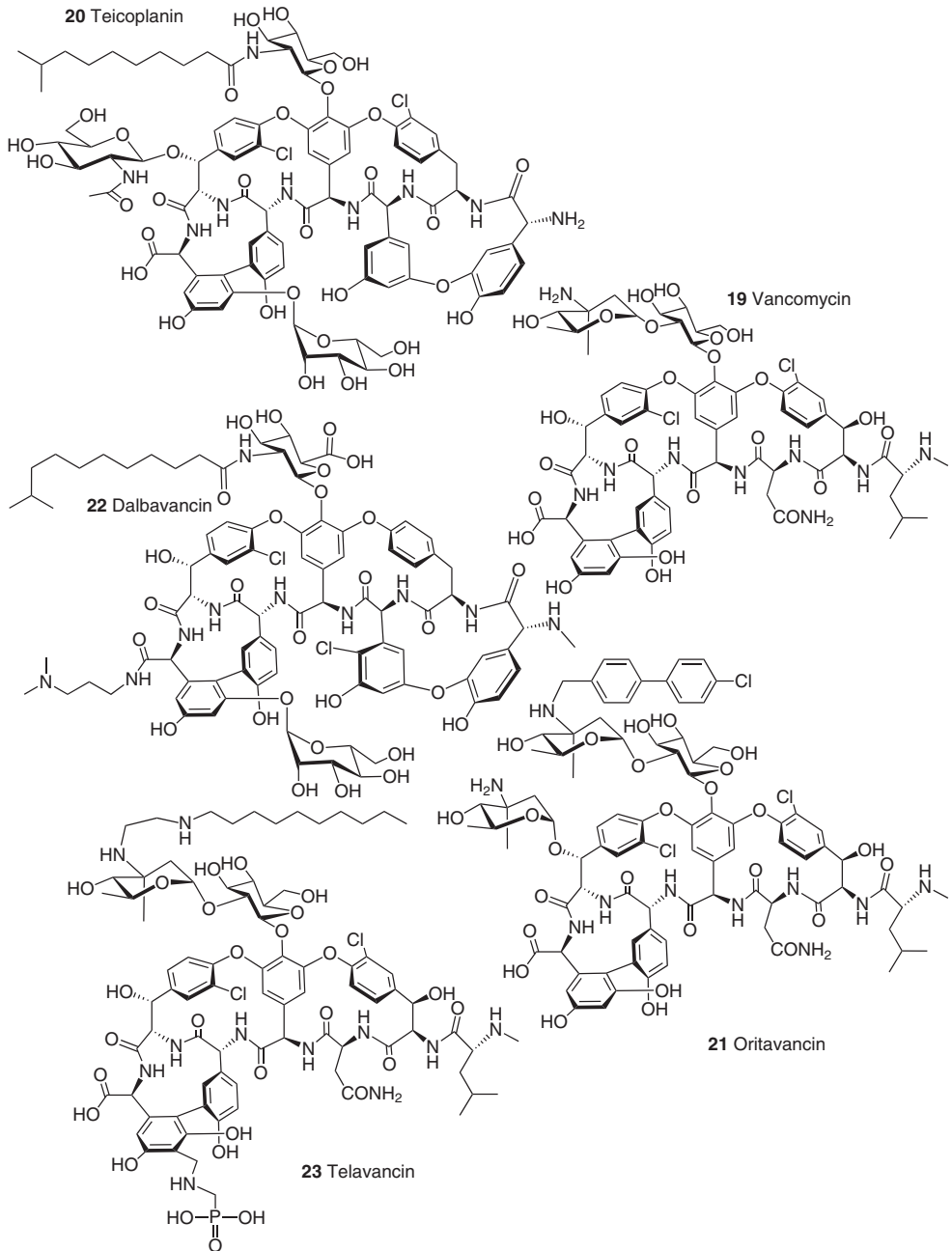


Figure 1.2 Dalbaheptide antibiotics.

practice in 1959, was isolated from *Streptomyces orientalis* (now *Amycolatopsis orientalis*) [4]. In 1988, teicoplanin **20** was also introduced. Glycopeptide antibiotics are restricted to treating gram-positive infections as they cannot penetrate the outer membrane of gram-negative bacteria. As vancomycin has been increasingly used for the treatment of a wide range of infections, second-generation glycopeptides with improved profile over vancomycin were developed. Even though recently innovative synthetic methods allowed successful total syntheses of these complex structures, fermentation followed by semisynthetic modification remains the prevalent way to explore SARs and the only practicable route to bulk production of clinical candidates. In general, the presence of specific sugars is of vital importance for dalbaheptide activity as aglycones are uniformly less active. At the same time, most efforts to change the natural heptapeptide backbones have resulted in reduced activity. Nevertheless, modification of the natural structure has led to novel, resistance-breaking dalbaheptides that contain structural elements promoting dimerization, to tight binding with the biological target, and lipophilic side chains that enhance membrane anchoring. An additional amino sugar at residue 6 and aromatic chlorine substituents promote favorable dimerization, and substitution of the free carboxylate function by basic carboxamides increases the activity against staphylococci. From these studies, three semisynthetic second-generation drugs have been advanced to clinical development. Oritavancin **21**, derived from the vancomycin-related glycopeptide chloroeremomycin, dalbavancin **22**, a derivative of the teicoplanin-related glycopeptide A40926, and telavancin **23** were approved by the Food and Drug Administration (FDA) in the United States in 2009 [10, 11].

1.4.2

Lantibiotics

Lantibiotics are small peptides (19–38 amino acids) produced mostly from strains belonging to the Firmicutes and, to a lesser extent, to the Actinobacteria, that undergo extensive posttranslational modifications to yield the active structures. The modifications common to all lantibiotics involve the dehydration of serine and threonine residues to yield 2,3-didehydroalanine (Dha) and (Z)-2,3-didehydrobutyrine (Dhb), respectively (Figure 1.3). This is followed by the stereospecific intramolecular addition of a cysteine residue onto Dha or Dhb to form a lanthionine (Lan) or methyllanthionine (MeLan) bridge, respectively. The term *lantibiotic* is, in fact, derived from Lan-containing antibiotics. Other modifications can be present on these molecules: for instance, C-terminal Cys residues may form S-aminovinylcysteine (AviCys) while N-terminal residues can contain 2-oxopropionyl (OPr) and 2-oxobutyryl groups (OBu). Their antimicrobial activity is limited to gram-positive bacteria; the prototype molecule is nisin **24**, discovered in the 1920s and used as a food preservative for 40 years [12]. Lantibiotics are divided into two classes according to their biogenesis: Lan formation in class I compounds requires two separate enzymes, a dehydratase and a cyclase, whereas a single enzyme carries both activities for class II lantibiotics. Although compounds from both classes exert their

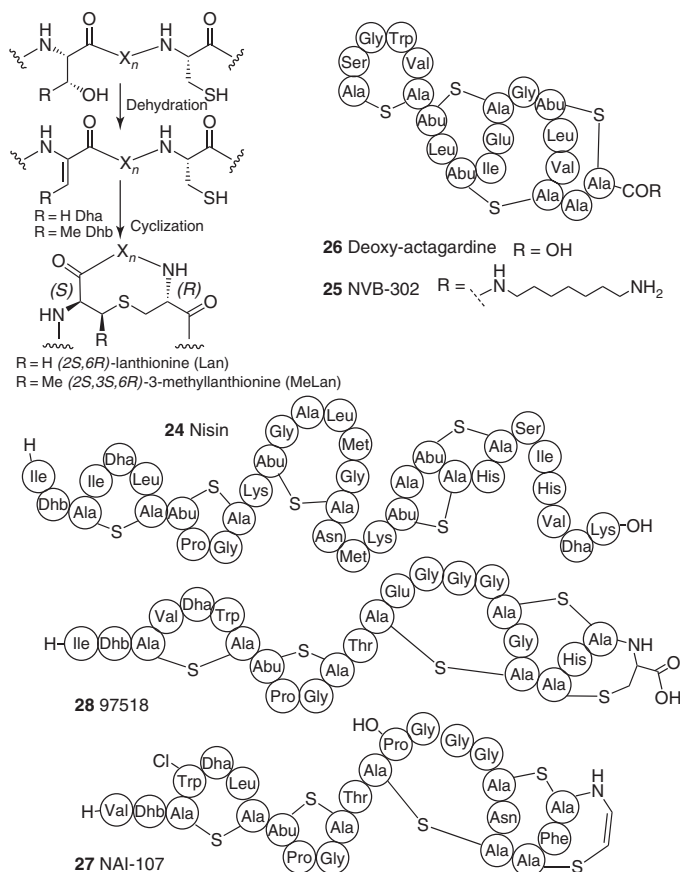


Figure 1.3 Lantibiotics.

antimicrobial activity by binding to Lipid II, thus inhibiting cell-wall biosynthesis, they do so by binding to different portions of this key peptidoglycan intermediate. Moreover, lantibiotics bind Lipid II at a site different from that affected by vancomycin and related glycopeptides, and they are active against multidrug-resistant (MDR) gram-positive pathogens and have attracted attention as potential drug candidates. The compound NVB302 **25**, a semisynthetic derivative of deoxyactagardine B **26**, is currently a developmental candidate [13]. Independently, a screening program designed to detect cell-wall-inhibiting compounds turned out to be very effective in identifying lantibiotics [14]. Among the new lantibiotics identified, the most active compound was NAI-107 **27**, containing two previously unknown modifications: a chlorinated tryptophan and a mono- or dihydroxylated proline. It is currently a developmental candidate for the treatment of nosocomial infections by gram-positive pathogens [15]. The same screening program led to the identification of additional class I lantibiotics from actinomycetes. Among them, the compound 97518 **28** is structurally related to NAI-107 but contains two carboxylic acids [16]

(the unmodified carboxy-terminal amino acid and an aspartic residue) and afforded improved derivatives by chemical modification of the acidic residues [17].

1.5

Cyclic Peptides

For simplicity, all cyclic peptides are grouped in this family (Figure 1.4 and Figure 1.5). Nevertheless, while the first described gramicidin S is a simple

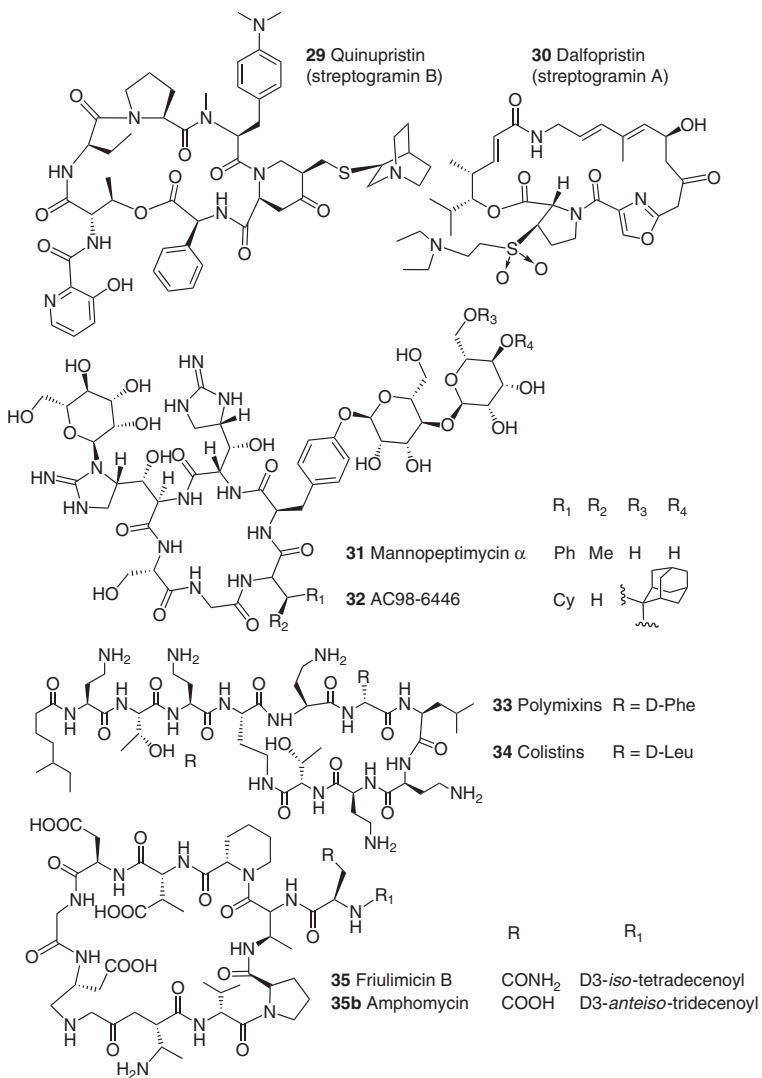


Figure 1.4 Cyclic peptide antibiotics (part I).

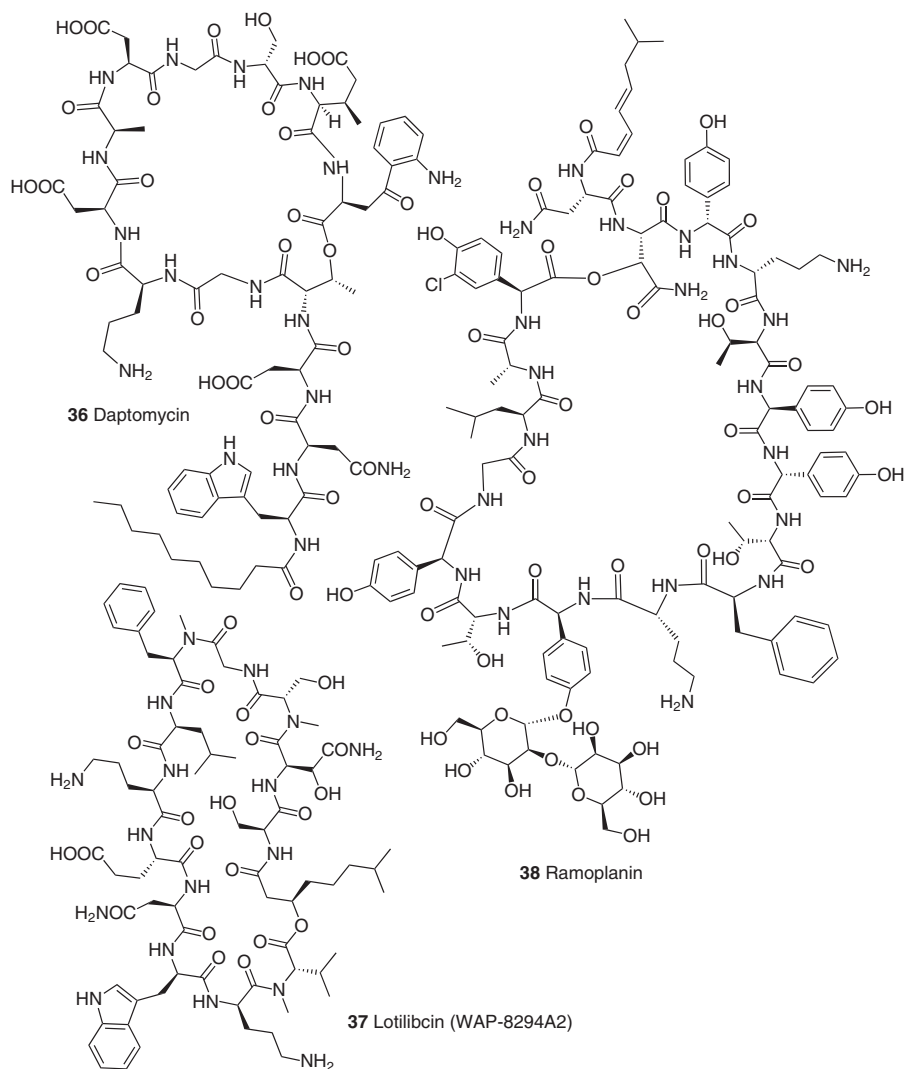


Figure 1.5 Cyclic peptide antibiotics (part II).

cyclopeptide, the later described antibiotics are more complex structures containing additional chemical groups that identify the molecules as glycosylated peptides when they contain sugar moieties (mannopeptimycin 31), lipopeptides when they contain a lipophilic side chain (polymixin 33, friulimicin 35), lipodepsipeptides when apart from the lipophilic chain a lactone is present in the cycle (daptomycin 36, lotilbicin 37), and glycolipodepsipeptide when all these characteristics are present (Ramoplanin 38). Gramicidin S is an antibiotic effective against some gram-positive and gram-negative bacteria as well as some fungi, which was discovered in 1942 and produced by the gram-positive bacterium *B. brevis*. Gramicidin S is

a cyclodecapeptide, constructed as two identical pentapeptides joined head to tail, formally written as cyclo(-Val-Orn-Leu-D-Phe-Pro)₂. Streptogramins are natural products produced by various members of the *Streptomyces* genus. This family of antibiotics consists of two subgroups, A and B, which are simultaneously produced in a ratio of roughly 70 : 30 [18]. Both subgroups inhibit protein synthesis by binding to the ribosome. Group A streptogramins are cyclic polyunsaturated macrolactones. Structural variations in type A streptogramins can arise from desaturation of the proline residue and by its substitution for alanine or cysteine residue. Examples of group A streptogramins are pristinamycin IIA (same as virginiamycin M1), madumycin II, and the semisynthetic derivative dalfopristin **29**. Group B streptogramins are cyclic hepta- or hexadepsipeptides, for example, pristinamycin IA, virginiamycin S, the semisynthetic quinupristin **30**. The invariant N-terminal threonine residue is N-acetylated with 3-hydroxypicolinic acid and forms a cyclizing ester linkage with the C-terminal carboxyl group of the peptide via its secondary hydroxyl group. Synercid (composed of a mixture of quinupristin and dalfopristin) is not orally available and is administered by intravenous routes. Efforts have therefore been made to generate new orally active streptogramins. In particular, a new oral streptogramin, designated NXL-103, has been shown to be very effective against a number of gram-positive and gram-negative organisms. Mannopectimycins [19] are glycosylated cyclic hexapeptides that contain both stereoisomers of the unusual amino acid β-hydroxy-enduracididine. They also contain an unusual N-glycosidic bond, which links a mannose sugar to one of the β-hydroxy-enduracididine residues. They were originally isolated in the 1950s from *Streptomyces hygroscopicus* but the chemical complexity and the lack of broad-spectrum activity reduced prospects for further development. Mannopectimycin **31** affects cell-wall biosynthesis and recently renewed interest in it has derived from its activity against MDR gram-positive pathogens. SAR data derived from the natural congeners, chemical derivatization, precursor-directed biosynthesis, and pathway engineering were employed for optimization [20]. These data demonstrated that antibacterial activity was enhanced by hydrophobic O-acylation of either of the two O-mannoses, particularly the terminal one, while it was reduced by esterification of the N-linked mannose or serine moieties. AC98-6446 **32** represents an optimized lead obtained by adamantyl ketalization of a cyclohexyl analog prepared by directed biosynthesis. Polimixins **33** and colistins **34** have a general structure consisting of a cyclic peptide with a long hydrophobic tail [21, 22]. They are produced by the gram-positive *Bacillus polymyxa* and are selectively toxic for gram-negative bacteria owing to their specificity for the lipopolysaccharide (LPS) molecule that characterizes many gram-negative outer membranes. The hydrophobic tail is important in causing membrane damage, suggesting a detergent-like mode of action. Polymixin nonapeptide, devoid of the hydrophobic tail, still binds to LPS, and causes some degree of membrane disorganization but no longer kills the bacterial cell. Polymixin B (colistin) was approved for clinical use in 1958 but its systemic toxicity, particularly nephrotoxicity, has limited its use to topical applications for the most part. Nevertheless, currently, polymyxins have been revived to treat infections due to multiply resistant gram-negative bacteria. Friulimicin B **35**

consists of a macrocyclic decapeptide core with an exocyclic asparagine acylated with a branched unsaturated lipophilic chain. Structurally, friulimicin belongs to the amphomycin family of cyclic lipopeptides, whose members differ in amino acids and fatty acid substituent. The correct structure of amphomycin (**35b**) was actually established almost 50 years after its discovery, along with friulimicin characterization. These studies revealed that the friulimicin producer *Actinoplanes friuliensis* makes macrocyclic decapeptides with an exocyclic acylated aspartic residue, identical to previously described amphomycin, tsushimycin, parvuline, and aspartocin, as well as compounds with an exocyclic asparagine, such as friulimicin [23]. Notwithstanding the structural similarity to daptomycin, amphomycin has a different mechanism of action; it has long been known to inhibit cell-wall biosynthesis and has completed phase I clinical trials. Daptomycin **36** is a cyclic lipodepsipeptide produced by *Streptomyces roseosporus* consisting of 13 amino acid cyclic peptides with a decanoyl side chain [24]. Discovered in the late 1980s, it is the first lipopeptide approved for clinical use (2003) in the treatment of gram-positive infections. Daptomycin acts on the membrane and causes rapid depolarization, resulting in a loss of membrane potential leading to inhibition of macromolecular syntheses and ultimately bacterial cell death. Its distinct mechanism of action means that it may be useful in treating infections caused by MDR bacteria. Lotilibcin (WAP-8294A2) **37** is a complex of 20 closely related components produced by a gram-negative bacterium *Lysobacter* sp. They are cyclic depsipeptides containing 12 amino acid residues and one 3-hydroxy-fatty acid residue. WAP-8294A2 was isolated as the major component, and showed a strong activity against gram-positive bacteria without posing any cross-resistance [6]. Ramoplanin **38** is a glycolipodepsipeptide antibiotic isolated from fermentation of *Actinoplanes* sp. containing 17 amino acids and a mixture of L and D amino acids as well as several nonproteinogenic side chains [25]. The first amino acid in the depsipeptide is acylated at the amino terminus with a lipid unsaturated substituent slightly different for three congeners. It is active against gram-positive aerobic and anaerobic bacteria, including vancomycin-resistant enterococci. Ramoplanin inhibits bacterial cell-wall biosynthesis by a mechanism different from those of other cell-wall synthesis and therefore does not show cross-resistance with them. Because of its potent antimicrobial activity, ramoplanin could be an effective antibiotic for treating serious gram-positive infections. However, it showed poor local tolerability upon intravenous injection and it is under development for prevention and treatment of *Clostridium difficile*-associated diarrhea, acting locally by decolonizing the gut. Semisynthetic derivatives of the natural molecules have been produced by selective removal and replacement of the original fatty acid chain with different chemical residues [26].

1.6

Thiazoly]peptides

Thiazoly]peptides are highly modified, ribosomally synthesized peptides that inhibit bacterial protein synthesis. They are characterized by a sulfur-containing

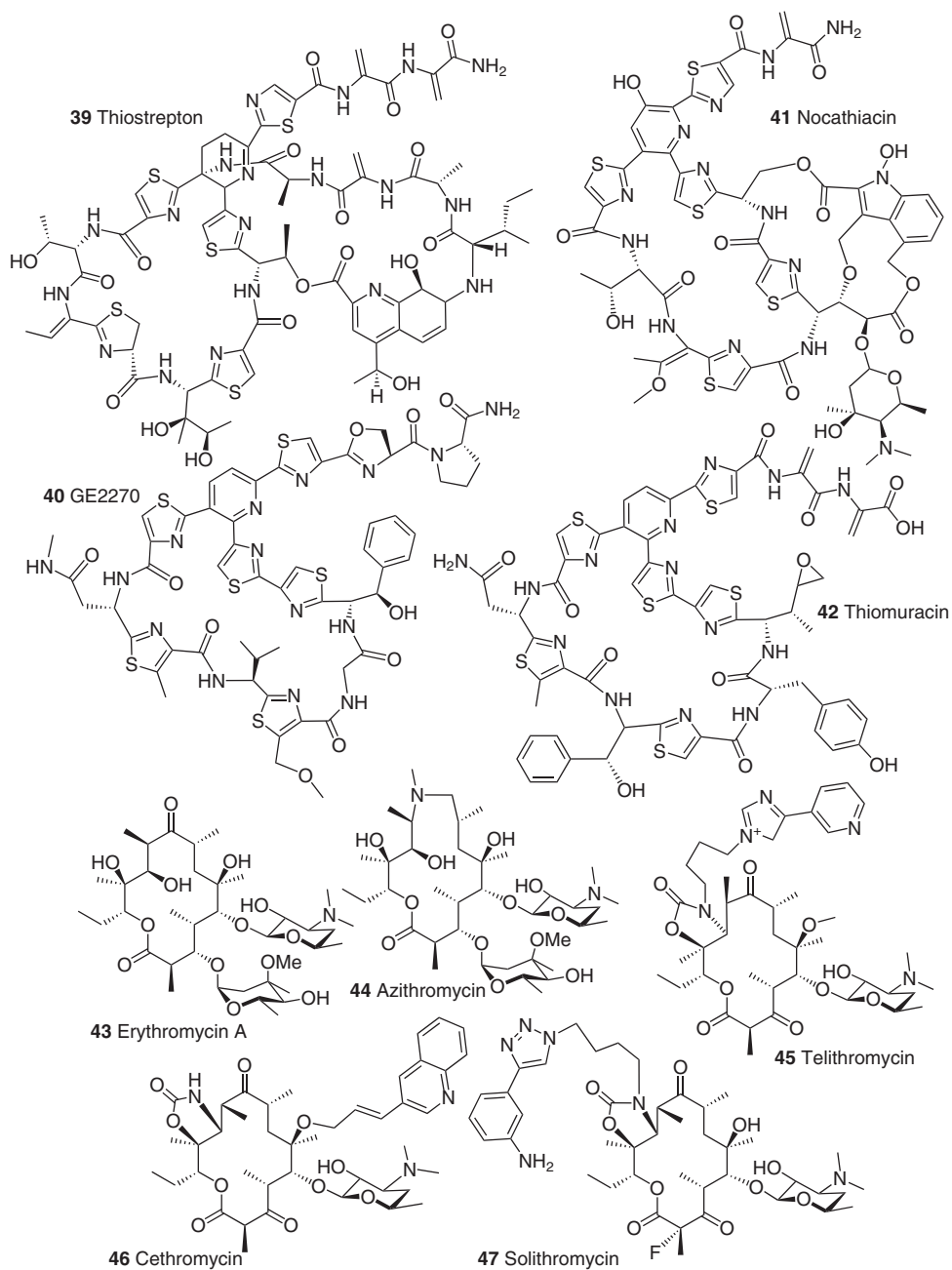


Figure 1.6 Thiazolylopeptide and macrolide antibiotics.

macrocyclic structure, which possess a tri- or tetra-substituted nitrogen-containing heterocycle core (Figure 1.6). Micrococcin was the first thiopeptide ever discovered (1948); it was produced by a *Micrococcus* sp. Other members of this class are produced by *Streptomyces* (thiostreptone **39**) and *Planobispora* sp. (GE2270 **40**). Nearly all of the thiopeptides inhibit protein synthesis; however, their cellular targets are distinct. For example, the structurally complex polycycles of nocathiacin **41** [27] and thiostrepton **39** bind to the 23S ribosomal ribonucleic acid (rRNA) component of the bacterial 50S ribosomal subunit, while GE2270 **40** and the thiomuracin **42** monocycles target the elongation factor Tu [28]. Most thiazolylpeptides show potent activity against gram-positive pathogens and this unique class of thiopeptides represents a significant and promising lead for antibiotic drug discovery, yet their poor solubility has limited clinical progress; only a derivative of GE2270 has entered clinical trials for the topical treatment of acne (NAI-Acne), in which the natural carboxy terminal is replaced by a semisynthetic amide residue [11]. Additional novel derivatives of GE2270 have recently been identified, where the natural carboxy-terminal amino acids are replaced by cycloalkylcarboxylic acid side chains by amide or urethane bond [29], and novel water-soluble derivatives of nocathiacin were also recently reported [27].

1.7

Macrolactones

1.7.1

Macrolides

Macrolides (Figure 1.6) are composed of a macrolacton, usually of 14–16 atoms, and at least 2 neutral- or amino sugars linked to the macrocycle, usually cladinose and desosoamine. Erythromycin A **43**, the prototype of this class, was first isolated from *Streptomyces erythreus* in 1952 [4]. Since their discovery, a significant number of new natural and semisynthetic derivatives have been produced. Despite the availability of total synthesis tools, semisynthesis still remains the only possibility for all marketed macrolides; nevertheless, molecular diversity was obtained in macrolides, not only by classical semisynthesis but also by combinatorial biosynthesis through modification of the polyketide biosynthetic machinery [4]. Among the most interesting semisynthetic derivatives, the azalides, obtained by Beckmann rearrangement from erythromycin A, have increased activity against gram-negative bacteria. Among them, azytromycin **44** was commercialized at the end of the 1980s. More recently, to overcome the several mechanisms involved in the resistance against this class, new macrolides named ketolides were rediscovered, in which 3-cladinose, erroneously considered for many years as a crucial structural element for antibiotic activity, is replaced with a 3-ketone substituent. Novel ketolides were demonstrated to have increased stability in acidic media and potent activity against erythromycin- and penicillin-resistant enterococci together with an enhanced pharmacokinetic profile. Among them, telithromycin **45** was the

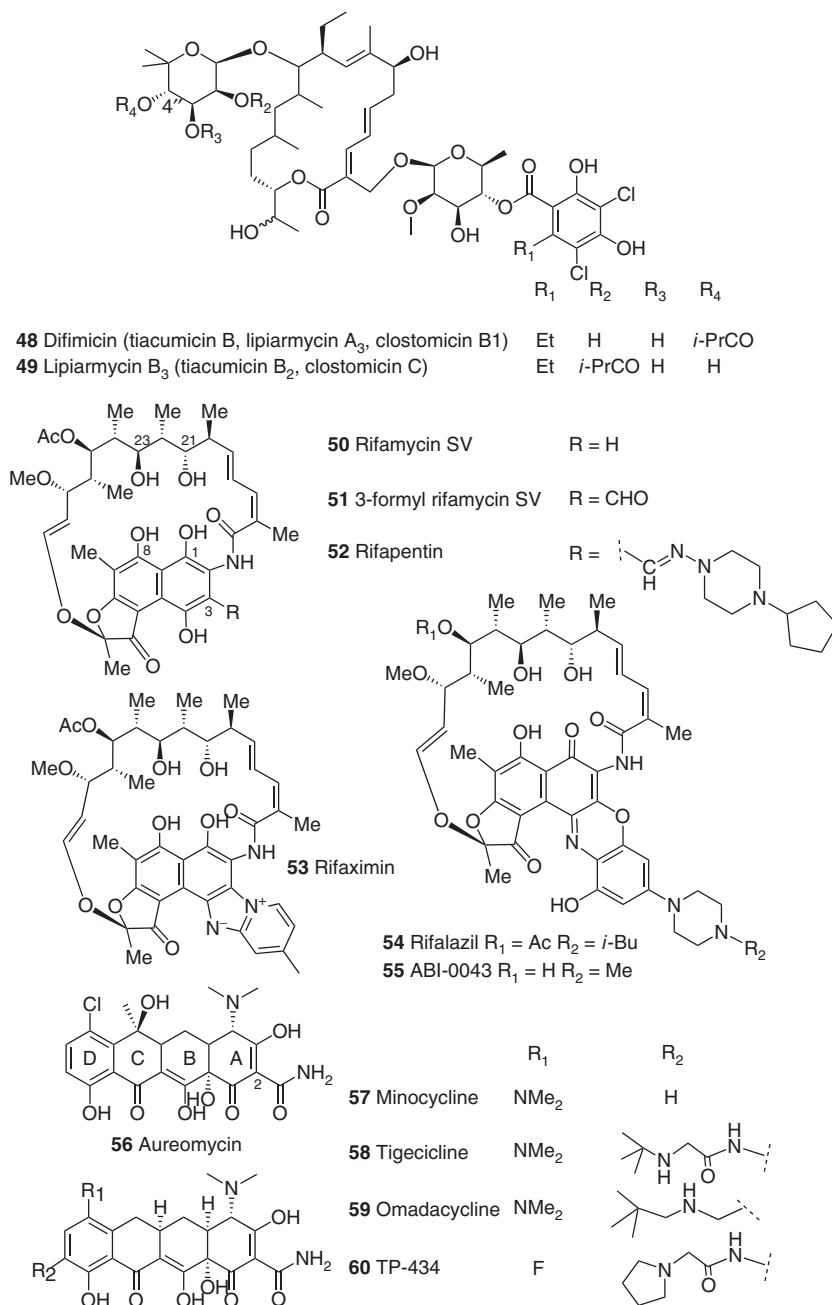


Figure 1.7 Macrocyclic antibiotics, rifamycins, and tetracyclines.

first ketolide approved for clinical use in the 2000s. Further improvement led to cethromycin **46** and solithromycin **47** as lead compounds, currently under clinical development [3]. Both are characterized by the presence of a cyclic carbamate group at the 11, 12-position that enhances the activity against susceptible and resistant strains by stabilizing the ketolide conformation.

1.7.2

Difimicin

Difimicin **48** (Figure 1.7) belongs to an 18-member family of actinomycete-produced macrocycles, independently discovered under the names of lipiarmycin, clostomycin, and tiacumicin [13]. Compounds in the family differ for variations in the macrolide ring and for the nature and position of the acyl residue esterified on the sugars, with the major component carrying an isopropyl ester at position 4". Among the natural congeners, lipiarmycin B **49** is less active than lipiarmycin A against all bacterial species, thus indicating that the position of the isobutyl residue on methyl rhamnose affects *in vitro* activity. Difimicin is a potent inhibitor of bacterial RNA polymerase (RNAP) and is currently under registration for the treatment of *C. difficile* infections.

1.8

Ansamycins–Rifamycins

The class of ansamycins is characterized by a cyclic structure in which an aliphatic chain forms a bridge between two nonadjacent positions of a cyclic π -system, similar to the handle of a basket or ansa (in Latin, hence the name). They are produced by strains of several genera of the order *Actinomycetales*. The most important ansamycins are rifamycins (Figure 1.7). They have an aliphatic ansa chain constituted of 17 atoms, are antibacterial, and selectively inhibit RNA polymerase. Following the first rifamycin isolation in 1957 (rifamycin SV **50**), extensive programs of semisynthesis led to the preparation and evaluation of a large number of rifamycin analogs with the aim of obtaining a compound with better oral absorption, more prolonged antibacterial levels in blood, and greater antimicrobial activity [30]. These studies gave important information on the SAR in rifamycins. The minimal requirements for antibiotic activity appeared to be the presence of the two hydroxyls at C₂₁ and C₂₃ positions of the ansa chain and the two polar groups at C₁ and C₈ positions of the naphthoquinonic nucleus, together with a conformation of the ansa chain that resulted in certain specific geometric relations among these four functional groups. Position 3 of the aromatic nucleus has been extensively derivatized, mainly starting from the readily available intermediate 3-formyl rifamycin **51** resulting in the synthesis of interesting compounds, among them rifapentin **52**, currently used for the treatment of tuberculosis in the United States, rifaximin **53**, and rifalazil **54**. Novel benzoxazinorifamycins have been recently synthesized and screened. Among them, novel derivatives (ABI-0043 **55**

is the main example) that possess both the ability to suppress the emergence of rifamycin-resistant mutants and show increased activity against mutants resistant to other rifamycins have been identified [30].

1.9

Tetracyclines

Tetracyclines are characterized by a polycyclic structure consisting of a highly functionalized and partially reduced naphthacene (Figure 1.7). They are usually produced by strains of *Streptomyces aureofaciens* and *Streptomyces rimosus* and, more recently, by *Micromonospora* and *Actinomadura brunea*. These molecules bind to the ribosome-inhibiting protein synthesis and are classified as broad-spectrum antibiotics. The first member of the group chlorotetracycline (aureomycin **56**) was discovered in the late 1940s. The first structural variations of the basic skeleton, obtained by semisynthesis from the natural precursor, were generally related to the C-5, C-6, C-7, and C-8 carbons and the carbamoyl group at position C-2 [31]. Since the 1970s, when minocycline **57** was approved, only tigecycline **58** has been introduced, in 2005, to treat infections resistant to other antimicrobials [32]. Nevertheless, the medicinal chemistry and semisynthesis of newer analogs have recently undergone a renaissance; moreover, total synthesis has become available, giving access to a broad range of tetracyclines that would be inaccessible by semisynthesis and provides a powerful engine for the discovery of new tetracyclines [33]. Among the new derivatives, omadacycline **59** (PTK-0796) is in phase III while TP-434 **60** is currently in phase II trials [3].

1.10

Oxazolidinones

Oxazolidinones are a new class of synthetic antibiotics, discovered in the 1980s (Figure 1.8) [18]. These compounds originated from an iterative medicinal chemistry effort starting with a series of racemic 5-halomethyl-3-phenyl-2-oxazolidinones with reported utility for treating a variety of plant diseases [34]. In 2000, the FDA approved linezolid **61**, which also showed a unique mechanism of protein synthesis inhibition [35]. Detailed SARs were obtained, leading to the identification of the molecular feature critical for the antibiotic activity. Linezolid is composed of an oxazolidin-2-one ring containing a critical (S) stereocenter in position 5. Aryl substitution of the nitrogen is also necessary for activity. Generally, the B-ring of oxazolidinone antibacterials contains a phenyl ring or fluorosubstituted phenyl rings. In addition to these, heterocyclic B-rings such as pyridine and pyrrole ring systems were also reported in the literature, showing limited improvements. In the most recent derivatives, additional rings C and D were introduced and/or modified following extensive chemical investigation. There are several oxazolidinone derivatives that are being clinically developed and several others that are in

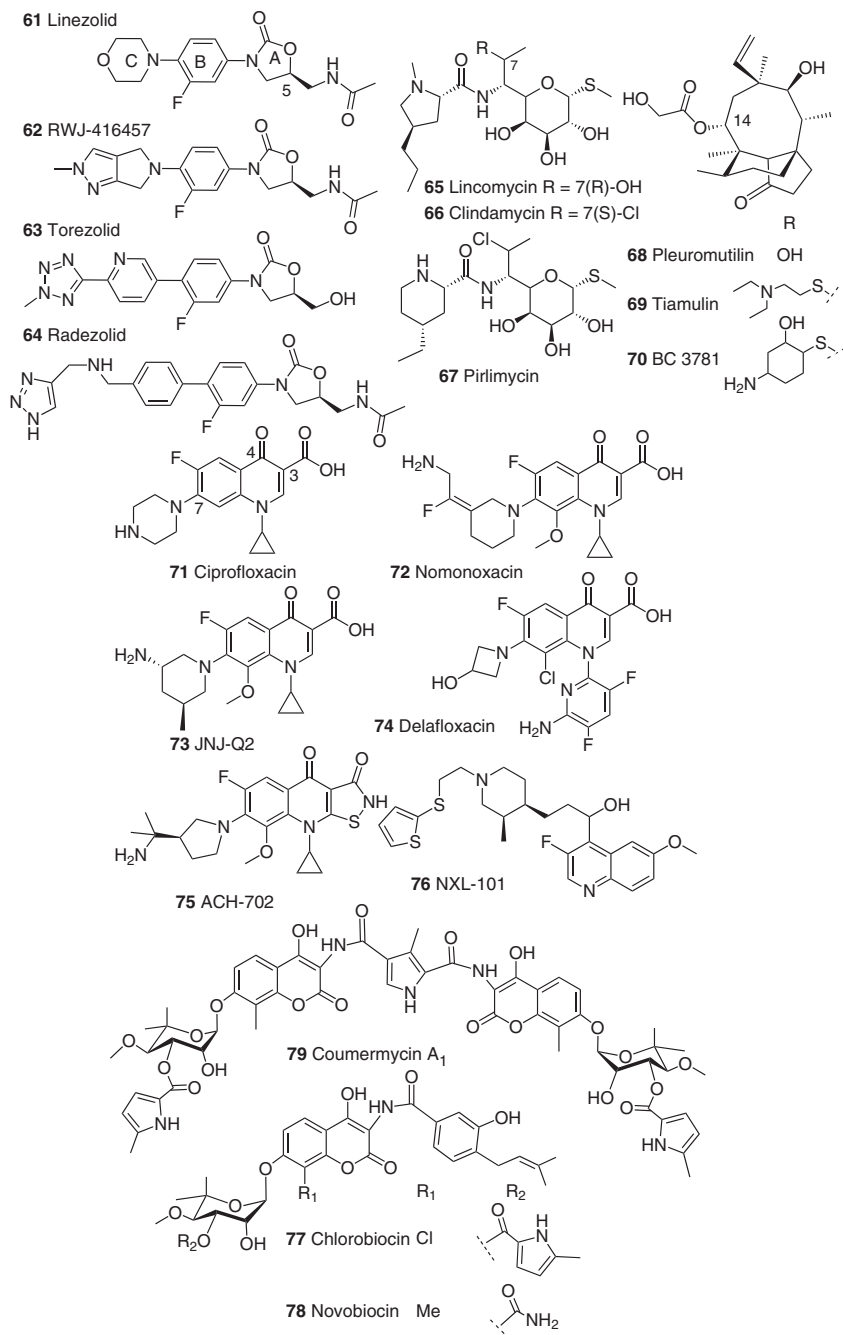


Figure 1.8 Oxazolidinones, lincosamides, pleuromutilins, and aminocoumarines.

preclinical development. Among the most interesting, RWJ-416457 **62** is modified on the C and D rings [36], torezolid **63** in addition to ring modification lacks the acetyl group [37], while radezolid **64** contains a new modification on the C-5 substituent [3].

1.11

Lincosamides

Lincomycin **65** (Figure 1.8) was isolated by fermentation of *Streptomyces lincolnensis* and was introduced in clinical medicine in 1960. Its semisynthetic analog clindamycin **66**, obtained by selective halogenation of the secondary alcohol in position 7, was also approved a few years later, in 1969 [4]. Lincosamides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit and show activity against most gram-positive and anaerobic bacteria but not against gram-negative and enterococci. Their use was limited by development of resistance due to methylation of the ribosomal target causing reduced binding affinity. Recently, new medicinal chemistry research programs were started to achieve second-generation lincosamide derivatives. Among the new products, pirlimycin **67** possesses an improved pharmacokinetic profile even if no improvement was observed in its spectrum of action. The molecule has been marketed for veterinary use.

1.12

Pleuromutilins

The diterpene antibiotic pleuromutilin **68** (Figure 1.8) from the fungus *Clitopilus* sp. was first discovered in 1951 and inhibits protein synthesis [38]. A series of derivatives was synthesized between 1963 and 1966, with a strong focus on variations in the C(14) side chain. Already at that time, it was recognized that the number of functional groups was small, which led to the consideration that an “activation” of the molecule via sulfonic acid esters at the C(14) atom would give the best opportunities for numerous exchange reactions. Of the derivatives generated, the mutilin esters of substituted thioglycolic acids demonstrated superior minimum inhibitory concentration (MIC) values. Further alterations within this group led to the development of the first veterinary pleuromutilin, tiamulin **69**, which was approved in 1979. Despite successful use in veterinary medicine, no derivative for systemic use in humans has been made. More recently, with the dramatic emergence of resistance to established antibacterial classes in the 1980s, significantly more attention has been given to the class of pleuromutilins to try to explore their potential for human use owing to its unique interaction with the bacterial 50S ribosomal subunit. Side-chain chemistry, in combination with extensive use of SARs derived from more than 1000 pleuromutilin derivatives, has led to the discovery of BC-3781 **70**, the very first systemic pleuromutilin recently tested successfully in patients in a phase II trial [39].

1.13

Quinolones

The quinolones (Figure 1.8) are a family of synthetic broad-spectrum antibiotics. Nalidixic acid, introduced into clinic practice in 1962, is considered to be the predecessor of all members of the quinolone family. The basic structure consists of an N-1 alkylated 3-carboxypyrid-4-one ring fused to another aromatic ring, which may contain various substituents. Quinolones inhibit two essential bacterial enzymes: DNA gyrase and topoisomerase IV to varying extents depending on the pathogen. Substitutions vary by drug and may influence activity. The 1-position can include small alkyl groups or an aryl group. The 2-position will maintain activity when it is either a carbon or nitrogen atom. Positions 3 and 4 are critical and must not be altered from the unsubstituted carboxylic acid and ketone, respectively. Substitutions are usually made at positions 5, 6, 7, and 8 to improve activity. Most newly reported quinolones have modifications of the crucial 7-position (piperazine group for ciprofloxacin **71**). The majority of quinolones in clinical use belong to the subset fluoroquinolones, which have a fluorine atom attached to the central ring system, typically at the 6-position or C-7 position. In fact, fluorine, chlorine, and methyl all appear to show improvement, with 6-fluoro giving the most significant improvement [40]. Despite the fact that the use of quinolones has been associated with increased incidence of MRSA, several new members of this class are under development: nemonoxacin **72**, JNJ-Q2 **73**, delafloxacin **74** [6]. Related compounds isothiazoloquinolones (ITQs) were first described by Abbott 20 years ago. They are one of the few quinolone analogs in which the carboxylic acid has been successfully replaced. ACH-702 **75** belongs to this group [41]. Strictly related to quinolone are quinolines, in which the aromatic nucleus does not contain the oxidation in position 4. NXL101 **76**, currently in phase I clinical trials, is representative of a new class of quinoline DNA gyrase and topoisomerase IV inhibitors with a gram-positive spectrum of antibacterial activity including MRSA- and fluoroquinolone-resistant isolates [42].

1.14

Aminocoumarins

Aminocoumarins such as clorobiocin **77**, novobiocin **78**, and coumeramycins produced by *Streptomyces* sp. are known inhibitors of GyrB ATPase (Figure 1.8) [43]. Their common characteristic structural moiety is a 3-amino-4,7-dihydroxycoumarin ring, substituted at position C-8 either with a methyl group or with a chlorine atom. In all three compounds, the 7-hydroxy group of the aminocoumarin moiety is glycosidically linked to an unusual deoxy sugar, 4-O-methyl-5-C-methyl-l-rhamnose, which is acylated at its 3-hydroxy group with a 5-methylpyrrole-2-carboxyl group or a carbamyl group. Coumermycin A₁ **79** is unique among the aminocoumarins in incorporating two 3-amino-4,7-dihydroxycoumarin moieties, which are connected through amide bonds to a central pyrrole unit-3-methylpyrrole-2,4-dicarboxylic

acid, resulting in a nearly but not completely symmetric molecule. Novobiocin was once marketed as an antibacterial but has since been withdrawn owing to toxicity. Several papers from Heide and colleagues over the past few years report new novobiocin analogs that have been isolated by selective manipulation of the biosynthetic gene clusters of *Streptomyces* [44].

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