CHAPTER 15

Emerging New Therapeutics Against Key Gram-Negative Pathogens

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Contents

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1. INTRODUCTION

Health-care-associated infections (HAIs) are a significant cause of morbidity and mortality and represent a major challenge to patient safety [1–4]. The estimated annual direct cost of treating HAIs in the United States ranges from 28.4 to 45 billion dollars resulting in a heavy burden on the public health system. The management of bacterial infections is becoming increasingly difficult due, in part, to the severity of illness and immune status of patients but more so due to the increased prevalence of multidrug-resistant (MDR) pathogens. Currently, the emergence of MDR Gram-positive and Gram-negative bacteria in both hospital and health-care-acquired infections is occurring [5]. Rice [6] recently described the most dangerous MDR bacteria as the ''ESKAPE'' pathogens *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species to emphasize that in both the developed and developing world, these pathogens more and more frequently escape the lethal killing action of most antibiotics. Adding to these concerns, the situation has been exacerbated by the stagnation in the development of novel antimicrobial agents to treat these pathogens. Moreover, the number of approved antibacterial drugs has steadily declined in the past decade as pointed out by the Infectious Diseases Society of America (IDSA) in a series of alarming reports [7–9], which also launched the 10×20 initiative for a global effort to develop 10 new antibacterial drugs by 2020 [7].

Antibiotic drug discovery in the past two decades has focused efforts on the development of antibiotics against Gram-positive bacteria and more specifically against multidrug-resistant *S. aureus* (MRSA). In contrast, treatment options against some MDR Gram-negative pathogens have become very limited [5], especially due to the emergence of resistance against the last resort antibiotics, colistin and polymyxin B [10]. There are several reasons which led to this alarming situation. Several major pharmaceutical companies have abandoned the antibacterial field probably frustrated by fading profitability margins [9,11]. Increasing hurdles and uncertainty in clinical trial design for successfully obtaining regulatory approval for novel antibiotics is another reason why companies have stepped out of this therapeutic area. Compounding the problem of limited financial resources is the fact that Gram-negative organisms are inherently difficult to kill. This is due in part to the outer membrane (OM) which is composed by up to 75% by lipopolysaccharides (LPSs) [12,13]. LPS is negatively charged which makes the OM of Gram-negative bacteria highly impermeable for many classes of antibiotics thereby providing the Gram-negative bacteria with a formidable shield to prevent entry of antibacterials. Moreover, these organisms are highly efficient at

upregulating, mutating, or acquiring genes that code for mechanisms of antibiotic resistance.

Recent data from the U.S. National Nosocomial Infections Surveillance (NNIS) system reported that in 2003, Gram-negative organisms are associated with hospital-acquired infection in intensive care units and that these pathogens are responsible for 66% of all cases of pneumonia, 24% of bloodstream infections, 42% of surgical site infections and 73 % of urinary tract infections [14].

Mid- to long-term strategies to prevent antimicrobial resistance in the intensive care unit include shorter courses of appropriate antibiotic treatment and narrowing of antimicrobial spectrum based on culture results [15]. A study aiming to assess the influence of broad-spectrum versus narrow-spectrum antibiotic prophylaxis in head-injured patients showed that narrow-spectrum prophylaxis was associated with lower rates of antibiotic resistance among the Gram-negative pathogens isolated from subsequent infections [16].

The focus of this review will be on compounds in late preclinical and clinical development and compounds derived from known and new classes of antibiotics which show promising activity against MDR Gram-negative bacteria. A major emphasis will be on compounds which exhibit a new mechanism of action and on anti-pseudomonal antibiotics. In addition, particular attention will be devoted to strategies which move away from the older model of identifying broad-spectrum antibiotics in favor of more focused, narrow-spectrum approaches.

2. NEW COMPOUNDS FROM KNOWN CLASSES

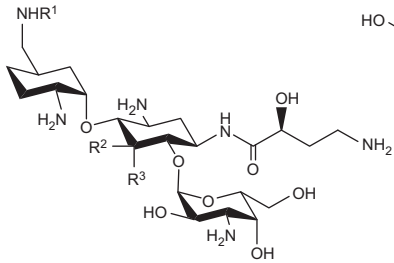
2.1. New aminoglycoside antibiotics

Since the discovery of streptomycin [17], aminoglycosides (AGs) have played a major role as efficacious broad-spectrum antibiotics. Despite vestibular and auditory toxicities observed as major side effects, streptomycin was remarkably successful and triggered the development of several other natural product-derived, semisynthetic AGs such as neomycin (1949); kanamycin (1957); paromomycin (1959); gentamycin (1963); tobramycin (1963); sisomycin (1970); and amikacin, isepamicin, netilmicin, and arbekacin (**1**) in the 1970s and early 1980s [18,19].

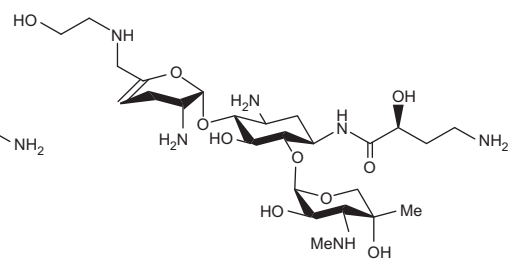
AGs bind to the A-site of ribosomal RNA and interfere with bacterial protein synthesis. Enzymes that inactivate AGs by modifying the molecule by methylation, N-acetylation, O-phosphorylation, or O-adenylation, and bacterial efflux pumps, constitute the two major resistance mechanisms. As an example, 16S rRNA methylases (such as ArmA and RmtC) confer resistance to all AGs [19].

Reported dose-limiting toxicities are neuromuscular blockade, oto- and nephrotoxicity.

The good activity of AGs against Gram-negative pathogens, including *P. aeruginosa*, however, has renewed the interest for developing new AG-derived antibiotics [19,20]. In a recent patent application [21], compounds such as **2** derived from arbekacin showed good broad-spectrum activity against Gram-negative and Gram-positive organisms including MRSA, and a twofold improved activity against *P. aeruginosa* (MIC values <4–8 μg/ml). Compound **3** (ACHN-490) was derived from sisomicin [18] and is currently in clinical evaluation for treatment of complicated urinary tract infections and acute pyelonephritis [19,22]. ACHN-490 demonstrated good activity against Gram-positive *Staphylococci* ($MIC_{90} = 2$ μg/ml) and a collection of Gram-negative clinical isolates of *P. aeruginosa*, *Escherichia coli*, *K. pneumoniae*, and *A. baumannii* [19]. In a Phase I clinical trial, ACHN-490 was well tolerated and exhibited linear and dose proportional pharmacokinetics (PK), while mild to moderate adverse events were reported [19]. It is important to note, however, that **3** is also susceptible to resistance *via* the same mechanisms as mentioned above for the class [23,24].



1 ($R^1 = H$; $R^2 = OH$; $R^3 = H$)
2 ($R^1 = Me$; $R^2 = H$; $R^3 = OH$)



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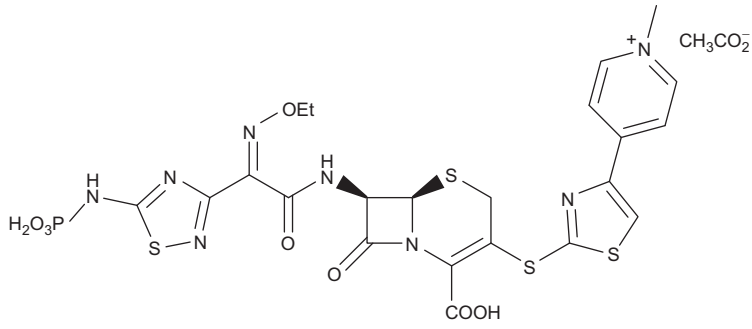
2.2. New β-lactam antibiotics

Since the discovery and wide therapeutic use of penicillin G, many β-lactam antibiotics have been successfully developed and commercialized [25]. The traditional β-lactam antibiotics comprise the penam (penicillin), penem, carbapenem, cephem (cephalosporins), carbacephem, and monobactam subfamilies. β-Lactams interfere with bacterial cell wall biosynthesis by inhibiting the final transpeptidation step in the synthesis of the peptidoglycan by transpeptidases known as penicillin-binding proteins (PBPs). There are two main mechanisms of resistance to

β-lactams: hydrolysis of the β-lactam ring *via* β-lactamases or the synthesis of altered PBPs with decreased sensitivity to β-lactams. The emergence of various classes of β-lactamases has become a serious issue, especially in the fight against Gram-negative bacteria.

In recent years, only a few novel broad-spectrum β-lactam antibiotics with improved activity against Gram-negative bacteria have been discovered. In addition, the combination of β-lactam antibiotics with β-lactamase inhibitors has emerged as a viable strategy to fight MDR Gram-negative bacteria. Among the more recent β-lactam antibiotics that are in late stage clinical development (Phase III) or being marketed are the two anti-MRSA cephalosporins, ceftobiprole and ceftaroline (**4**) [25]. Both compounds are considered fifth generation cephalosporins due to their pronounced anti-MRSA activity, but like the previous generation cephalosporins, they maintain a broad-spectrum activity against Gram-negative bacteria. However, like their predecessors, these cephalosporins do not overcome resistance from Gram-negative bacteria producing extended spectrum β-lactamases (ESBLs) [26,27]. More recently, ceftaroline has been described in combinations with other antibiotics such as amikacin and meropenem to have synergistic activities against cephalosporin-resistant Gram-negative bacteria [28]. Two more recent cephalosporins with enhanced anti-pseudomonal activity include **5** (CXA-101) [29,30] and **6**. CXA-101 has demonstrated potent activity toward *P. aeruginosa* including carbapenem-resistant isolates [31,32]. However, the compound displayed modest activity when tested against cephalosporin-resistant *P. aeruginosa* and against cephalosporin-resistant Enterobacteriaceae and *Bacteroides fragalis* isolates [33]. Compound **6** employs a catechol unit as an iron-chelating group which improves its entry into Gram-negative bacteria, particularly into *P. aeruginosa* [34,35]. CXA-101 has recently completed early clinical trials for safety and efficacy in patients with complicated urinary tract infections and is currently under investigation for treatment of complicated intra-abdominal infections with Gram-negative bacteria.



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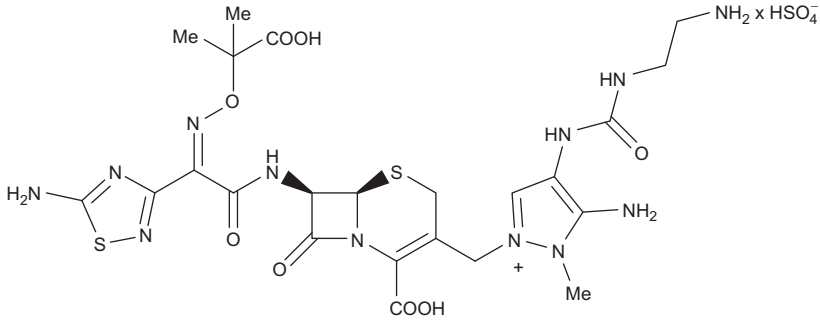

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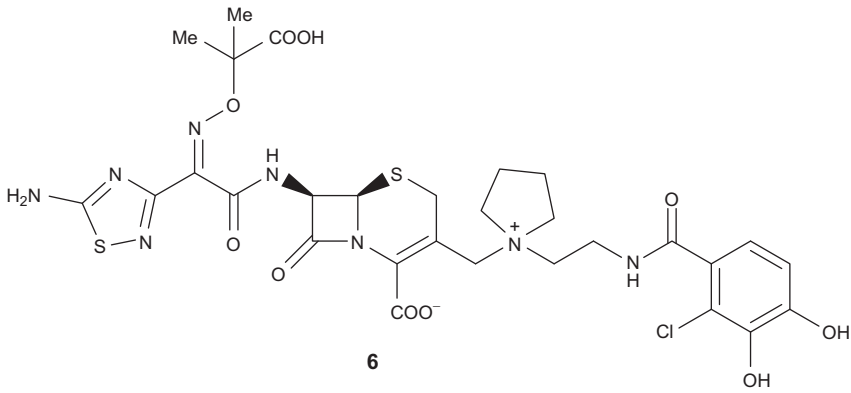

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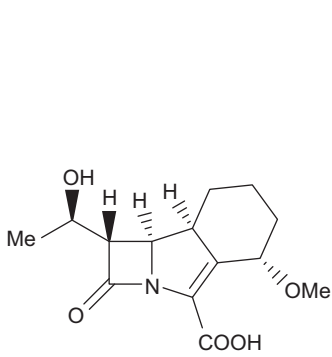
New tricyclic carbapenems such as **7** (LK-176) [36] are effective as inhibitors of β-lactamases of class C and also of class A by forming stable acyl enzyme complexes with low turnover rates [37]. Compound **7** demonstrated synergism with cefotaxim and ceftazidime against Enterobactericeae that produce class A and class C β-lactamases [25]. Similar

to **6**, some novel agents such as **8** (BAL30072) incorporate siderophores in their structure in order to facilitate the intracellular uptake by iron transport mechanisms [38]. In addition, the siderophore moiety of BAL30072 contributes directly to the good antimicrobial activity and the facilitated uptake appears to contribute significantly to the activity against *A. baumanni*. Compound **8** shows a broad-spectrum antibiotic activity including MDR *P. aeruginosa* and some carbapenem-resistant *Acinetobacter* spp. [38]. In recent years, several successful examples of combinations of β-lactam antibiotics with β-lactamase inhibitors such as **9** (tazobactam) and **10** (NXL104) have been described [25]. CXA-201 is a 2:1 combination of **5** and **9** that is effective against MDR *P. aeruginosa* and other Gram-negative pathogens and is currently in Phase II development [39]. Combinations of **10** with cefazidime and ceftaroline have also been described [25].



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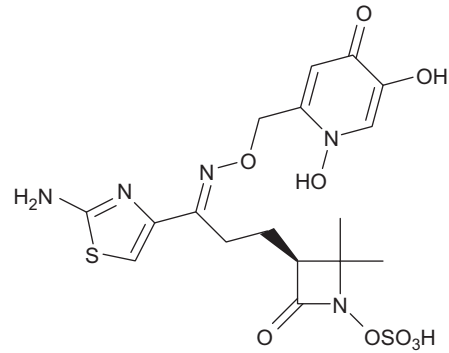

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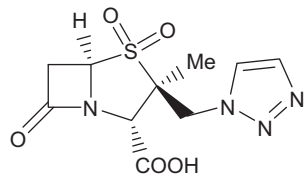

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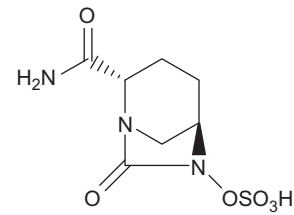

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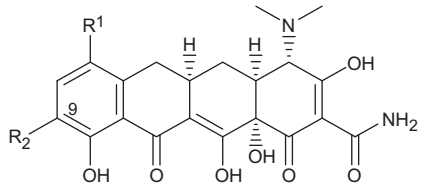
2.3. New tetracycline antibiotics

The tetracyclines were discovered in 1945 (chlortetracycline) and belong to one of the important classes of broad-spectrum antibiotics [40]. Two of the more common semisynthetic tetracyclines that have been marketed for decades are doxycycline and minocycline. The tetracyclines inhibit bacterial growth by inhibiting bacterial protein synthesis by preventing the association of aminoacyl-tRNA with bacterial ribosomes [41]. Resistance

to tetracyclines is mediated through three main mechanisms: efflux, reduced affinity to the target, as well as enzymatic inactivation. A number of tetracycline analogues have been designed to prevent the development of resistance toward tetracyclines. The glycylcyclines such as **11** (tigecycline) bind with a 5- to 100-fold higher affinity to 30S and 70S ribosomes than tetracyclines, respectively. In 2005, the FDA approved tigecycline for the treatment of complicated skin and soft tissue infections as well as complicated intra-abdominal infections [3,42]. Tigecycline is active against many Gram-positive bacteria, Gram-negative bacteria, and anaerobes—including MRSA, vancomycin-resistant *Enterococci* (VRE), drug-resistant *Streptococcus pneumoniae*, and Gram-negative pathogens of respiratory infections such as *Haemophilus influenzae*, *Moraxella catarrhalis*, Enterobacteriaceae, and MDR strains of *A. baumannii*. It is also active against *Mycoplasma pneumoniae*. However, tigecycline has limited activity against *Pseudomonas* spp. or *Proteus* spp. [43]. Additional analogues of **11** in clinical development include **12** (PTK-0796; BAY 73-6944), an aminomethylcycline, and more recently **13** (TP-434) [44]. A Phase III study of PTK-0796 in patients with complicated skin and skin structure infection (CSSSI) is planned.

Like tigecycline, these novel compounds overcome tetracycline resistance due to efflux pumps and/or ribosomal protection [45], and show a broad-spectrum activity toward both Gram-positive and Gram-negative pathogens. However, similar to tigecycline, these compounds lack good antibacterial activity against *P. aeruginosa*.



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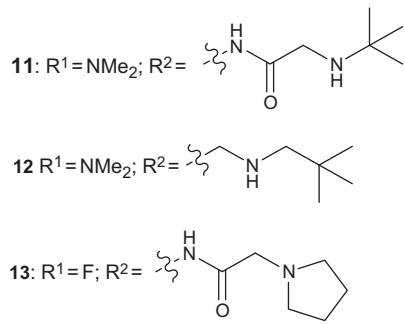
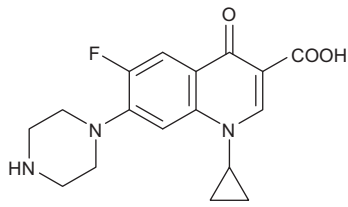


2.4. New quinolone antibiotics

The quinolone class is one of the most important classes of antibiotics identified in the past 50 years [46]. The discovery of fluoroquinolones in the 1980s constituted a breakthrough due to their excellent broad-spectrum activity that includes Gram-negative pathogens. Ciprofloxacin (**14**), levofloxacin, and moxifloxacin have become major pharmaceutical products. Quinolones target the bacterial type II topoisomerases, that is, DNA gyrase,

topoisomerase IV [47,48]. These heterotetrameric enzymes manipulate DNA topology by introduction of transient double-stranded breaks in bound DNA. Quinolone antibiotics bind to the enzyme complex and the cut DNA, which stabilizes this so-called cleavage complex and leads to accumulation and eventual release of double-stranded DNA breaks that are ultimately lethal to the cell because bacterial DNA synthesis is inhibited [49] .These enzymes are attractive as antibacterial targets as they are essential, common to all bacteria, and their human homologues are sufficiently different to achieve selectivity. Ciprofloxacin remains the most potent quinolone against Gram-negative bacteria and is effective against many susceptible strains of *P. aeruginosa* and *A. baumannii*. Despite potential toxicity issues and emergence of bacterial resistance, there is still enthusiasm for these antibiotics, especially in view of their activity against Gram-negative bacteria [46]. Quinolones that are in clinical development showing good activity against Gram-negative bacteria are finafloxacin (**15**) and nemonoxacin (**16**). Due to their broad-spectrum activity, quinolones have been tested against various infections. Compound **15** was in Phase II clinical trials for *Helicobacter pylori* and urinary tract infection indications and possesses antibacterial activity against ciprofloxacin-sensitive and -resistant *A. baumannii* strains [50,51]. Phase II trials for community-acquired pneumonia (CAP) and diabetic foot infections were recently completed for quinolone **16** with a favorable safety profile [52]. Among the preclinical compounds, quinolone **17** (WQ-3813) shows interesting activities against nosocomial pathogens MRSA, *E. coli*, and *A. baumannii* as well as major respiratory pathogens including MDR- and quinolone-resistant isolates [48]. It has the potential to be developed for the treatment of respiratory infections.



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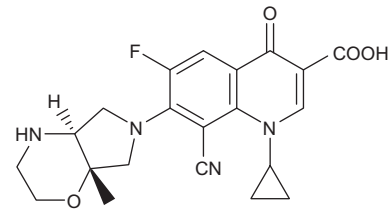

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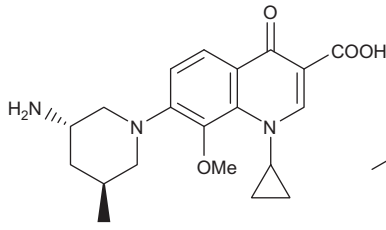

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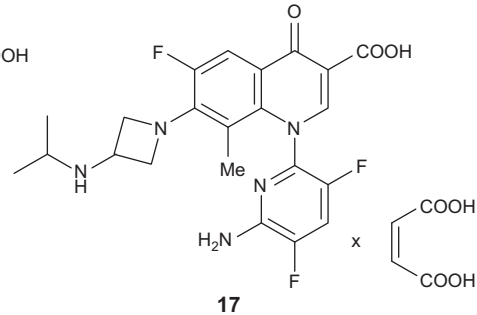

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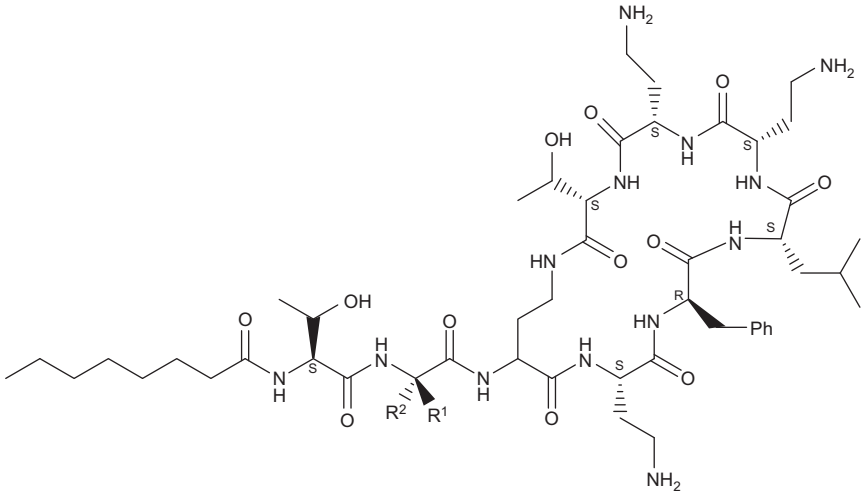
2.5. New antimicrobial peptides, lipopeptides, and natural product-derived antibiotics

Natural products have been a rich source for the discovery of new antibacterial drugs [53,54]. Among those, antimicrobial peptides (AMPs) [5,55] and lipopeptides [56] hold great promise to the identification and development of new antibiotics against MDR pathogens, including Gram-negative species.

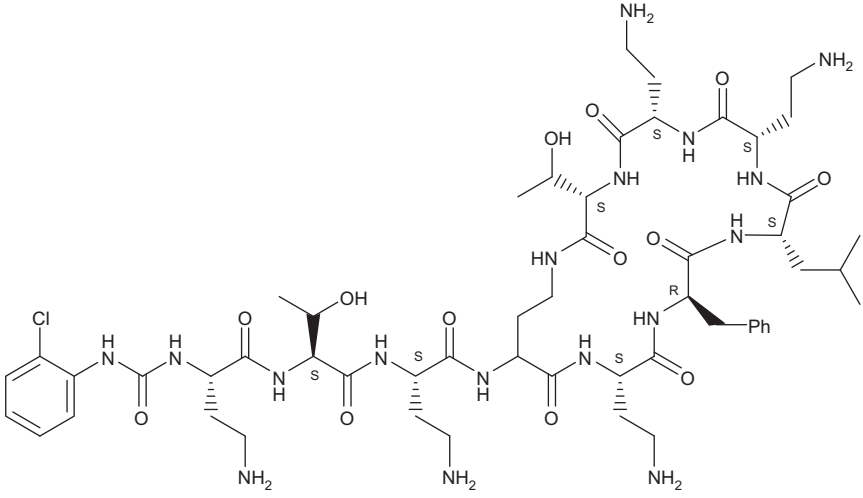
The polymyxin family of antibiotics was discovered in 1947 and comprises polymyxins A–E, where only polymyxins B and E (colistin) have been used clinically [54]. Polymyxins are highly active against a large panel of Gram-negative bacteria, including *P. aeruginosa* and *A. baumannii* [54,57]; however, they were abandoned as systemic therapy in the 1970s because of renal toxicity [10]. Due to the rapid emergence of MDR Gram-negative bacteria, in recent years they have regained importance and are now regarded as last resort antibiotics. However, colistin-resistant *A. baumannii* strains are emerging rapidly in recent years [57]. Hence, new polymyxin derivatives showing an improved toxicity profile and activity against these MDR clinical strains would be highly desirable. Alternatively, the discovery of novel antibiotics with a similar antibacterial profile as polymyxins but with a different mode of action would be desirable to overcome colistin resistance.

Two interesting new polymyxin-derived antibiotics **18** (NAB739) and **19** (NAB7061) have recently been described in preclinical studies [10,58]. Compound **18** shows a similar antimicrobial activity spectrum to polymyxin B or colistin; however, it has an overall net positive charge of $+3$, compared to $+5$ for the polymyxins, which could be favorable for reducing renal toxicity. NAB7061, similar to the polymyxin nonapeptide, lacks direct antimicrobial activity but reduces the MICs of many antibiotics when given in combination (*e.g.*, with rifampin and clarithromycin) for *E. coli*, *K. pneumoniae*, *K. oxytoca*, *E. freudii*, and *A. baumannii* [58]. NAB compounds **18** and **19** have decreased affinity in the isolated rat kidney brush border membrane assay in comparison to polymyxin B ($\sim$ 15-20%), which might be a predictive assay for kidney toxicity observed for polymyxins and AGs. The relevance of this finding for kidney toxicity *in vivo* remains to be seen [10]. Polymyxin B derivative **20** (CB-182,804) having a net charge of $+5$ shows activity against Gram-negative pathogens, including ESBLs and carbapenemases (KPCs)-producing strains [59]. Overall, the antibacterial spectrum of activity of CB-182,804 closely resembles that of colistin and polymyxin B [60]. *In vitro* killing kinetics of CB-182,804 showed that the compound had low MICs (0.5–2 μg/ml) and very good killing against 10 drug-susceptible and -resistant Gram-negative species [61].



18: $R^1 = CH_2OH$; $R^2 = H$

19: $R^1 = H$; $R^2 = CH_2CH_3$



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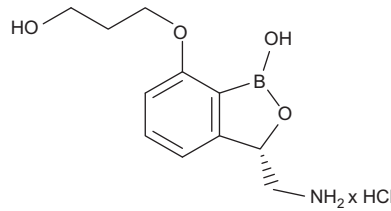
3. NOVEL COMPOUND CLASSES

3.1. Oxaboroles

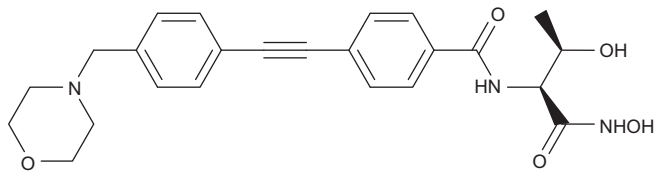
Oxaborole **21** (AN3365) belongs to a novel class of boron-containing antibiotics with good antimicrobial activity against a broad range of Gram-negative bacteria, including MDR *P. aeruginosa* ($MIC_{50/90} = 4/8$ μg/ml), wild-type *Acinetobacter* spp., and *Burkholderia cepacia* [62]. The oxaboroles block protein biosynthesis by inhibiting leucyl-tRNA synthetase *via* a unique mechanism of action [63]. Compound **21** completed a Phase I clinical trial [62] and holds promise for the treatment of Gram-negative bacterial infections against MDR pathogens.



21 (AN3365)

3.2. LpxC inhibitors

The zinc-dependent metalloaminase UDP-3-*O*-(*R*-3-hydroxymyristoyl)-N-acetylglucosamine deacylase (LpxC) is a promising target against Gram-negative bacteria as it is highly conserved, and many potent LpxC inhibitors have been described [64]. Among those, compound **22** (CHIR-090) shows antimicrobial activity against *P. aeruginosa* and *E. coli* comparable to tobramycin and ciprofloxacin [64].

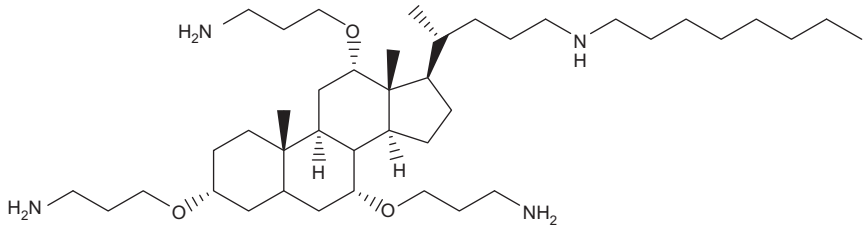


22 (CHIR-090)

3.3. Ceragenins (CSA-13)

Ceragenins are cholic acid-derived antimicrobial agents that mimic the activity of endogenous AMPs and act *via* membrane depolarization [5,65]. CSA-13 (**23**) is the most potent of the ceragenin class with broad-spectrum antimicrobial activity. MBCs for **23** against *E. coli* (minimal bactericidal

concentration (MBC)=1.5 μg/ml), *K. pneumoniae* (MBC = 2.5 μg/ml), and *P. aeruginosa* (MBC = 3.5 μg/ml) were described [65]. In particular, **23** shows also some activity against a MDR *P. aeruginosa* strain [66]. The *in vitro* activities of CSA-13, alone or in combination with colistin, tobramycin, and ciprofloxacin, were investigated using 50 *P. aeruginosa* isolates from CF patients. Synergistic interactions were mostly seen for CSA-13 in combination with colistin. Therefore, CSA-13 seems to be an interesting candidate for the treatment of *P. aeruginosa* strains in CF patients, alone or in combination. However, additional studies on safety, efficacy, and PK are needed [67].



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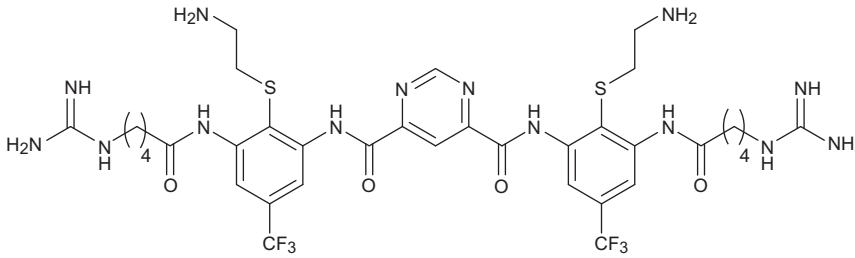
3.4. Peptide mimetics: PMX30063

In view of overcoming some unfavorable drug-like properties of AMPs such as low plasma stability and high hemolytic activity, new approaches have been utilized to design and synthesize peptide mimetics. Restrained antimicrobial arylamide foldamers such as **24** have been described in recent years [68].



24

Foldamers were designed to mimic amphiphilic structures observed in many α-helical- and β-hairpin-derived AMPs by a non-peptidic aryl amide scaffold. These compounds show a membranolytic mechanism of action which seems, however, to be more specific toward bacterial rather than mammalian membranes resulting in reduced hemolytic activity.

The most active compounds show broad-spectrum activity including activity against some Gram-negative bacteria.

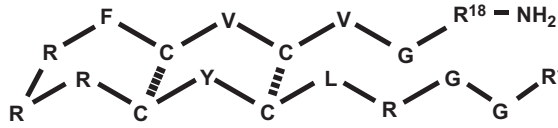
PMX30063 was derived from the foldamer concept and has entered clinical development in 2008 [69,70].

3.5. New β-hairpin mimetics targeting outer-membrane biogenesis of *P. aeruginosa*

AMPs such as protegrin I (**25**) show great potential in large part due to their activity against MDR Gram-negative bacteria [55] and low incidences of bacterial resistance formation. However, their clinical development as systemic drugs has so far been hampered by some unfavorable ADMET properties [5].

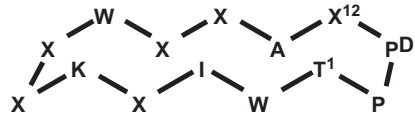
By transferring the protegrin I pharmacophore onto a cyclic 14-residue peptide β-hairpin mimetic scaffold [71,72], potent protegrin I analogues could be obtained [72]. Several rounds of optimization aimed at optimizing potency and ADMET properties yielded novel compounds such as **26** (POL7001) [73], which display potent and selective activity against a large panel of *P. aeruginosa* clinical strains, including many isolates from CF patients resistant to one or more classes of antibiotics. MIC_{90} for **26** was 0.25 μg/ml against a broad panel of clinical isolates including several MDR strains. *In vivo* efficacy of **26** was evaluated in a mouse septicemia infection model after dosing subcutaneously at 1 and 5 h after bacterial inoculation with either *P. aeruginosa* ATCC 9027 or ATCC 27853. POL7001 demonstrated excellent activity with ED_{50} in the range of 0.25–0.28 mg/kg as compared to gentamycin (used as a positive control), which showed an ED_{50} of 3.1 and 2.9 mg/kg, respectively [73].

Biochemical and genetic studies showed that these peptidomimetics are bactericidal, however, they act by a non-membranolytic mechanism of action. Instead, through the use of photoaffinity-labeled analogues, the putative target of these novel compounds was identified as the *Pseudomonas* OM protein, LptD [73,74]. LptD is a β-barrel OM protein widely distributed in Gram-negative bacteria that plays a role in the assembly of LPS in the outer leaflet of the outer membrane. LptD represents a novel target in antibiotic drug discovery and development, and its identification emphasizes the essential need to explore novel chemical approaches. One member of the β-hairpin mimetic family (POL7080) is currently under investigation in a Phase I study to assess its safety, tolerability, and pharmacokinetic profile in man for the intravenous administration route.



25 (Protegrin I)

C = cystein, F = phenylalanine, G = glycine, L = leucine, R = arginine, Y = tyrosine



26 (POL7001)

A = alanine, I = isoleucine, K = lysine, P = proline, T = threonine, X: L-2,4-diamino butyric acid

4. CONCLUSION

In this review, we have summarized the most promising antibacterial compounds currently being developed against Gram-negative bacteria. As a major caveat, most of these compounds in preclinical and early development are derived from established classes. Within the established drug classes, novel β-lactam antibiotics containing iron-chelating groups such as **8** seem promising. They use bacterial iron uptake mechanisms as a means to bypass the defense mechanisms of bacteria (''Trojan horse'' approach). These compounds show good activity against a range of MDR Gram-negative bacteria. Furthermore, several combinations of established β-lactam antibiotics such as ceftaroline and novel β-lactamase inhibitors such as **10** are emerging. The excellent activity of ciprofloxacin against a broad range of Gram-negative strains has triggered renewed interest in the development of new quinolones. Compound **15** is one of the most promising candidates. However, these new derivatives will encounter the well-established mechanisms which lead to resistance to previous members of the fluoroquinolone class. Furthermore, analogues of the last resort antimicrobial peptide colistin (*e.g.*, **18** and **20**) have been designed and studied by several academic groups and small Biotech companies. Whether these new compounds will show an improved therapeutic window *in vivo* is currently under investigation.

The search for novel antibiotics with a novel mechanism of action has been traditionally very difficult. In that respect, the discovery of the oxaboroles (*e.g.*, **21**) and of a new class of β-hairpin mimetics (*e.g.*, **26**)

constitutes highlights. Both compound classes exhibit novel, bacteria-specific mechanisms of action and may offer solutions to the emerging resistance problems seen with current antibiotics to combat serious and life-threatening infections by Gram-negative bacteria.

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