Clinically Approved Antibiotics from 2010 to 2022

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Clinically Approved Antibiotics from 2010 to 2022

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§SCS-DSM Award for best poster in Medicinal Chemistry

Abstract: This review discusses small-molecule antibiotics approved for clinical use in the time frame 2010–2022. This time span saw the approval of four synthetic antibiotics (bedaquiline, pretomanid, delafloxacin, tedizolid), nine natural product derivatives (ceftaroline fosamil, cefiderocol, plazomicin, omadacycline, eravacycline, sarecycline, lefamulin, dalbavancin, oritavancin), and one natural product (fidaxomicin).

Keywords: Antibiotics · Antimicrobial resistance · Natural products · Semisynthesis · Tuberculosis

Erik Jung received his bachelor's degree from the University of Freiburg followed by a 12-month internship in the Medicinal Chemistry Department of Hoffmann – La Roche. He then performed his Master thesis in the group of Prof. Dr. Karl Gademann (University of Zurich), supported by the Alfred-Werner scholarship. Currently he is pursuing his PhD studies in the Gademann group, focusing on the semi- and total synthesis of antibiotics.

1. Introduction

The rise of antimicrobial resistance and the associated impact on human health have often been referred to as the 'silent pandemic'. After a golden era of antibiotic discovery, a time of wide-spread resistance, a slowdown in the discovery of new antibiotic classes, and reduced financial incentives to develop new antibiotics all led to a dire situation. Facing this, antibiotic development is experiencing a renaissance.[1] In this review, we give a brief overview of fourteen small-molecule, new molecular entities approved by the FDA for the treatment of bacterial infections from 2010 to 2022. Among those, four are synthetic, nine are derived from natural products, and one is a natural product itself.

2. Antibiotics

2.1 *Synthetic Antibiotics (Fig. 1)*

2.1.1 *Bedaquiline (Sirturo®)*[2]

After decades without new anti-tubercular drugs, bedaquiline was the first new drug approved for the treatment of tuberculosis (TB).[3] Bedaquiline inhibits the mycobacterial ATP synthase by trapping the rotor, a new mode of action.[4] Following the results of a phase IIb trial, bedaquiline was granted accelerated approval for the treatment of serious conditions.[5] The concept of the randomized, controlled clinical trial was first established in the 1940s to evaluate TB treatments.[6] Even today, Phase III trials for new tuberculosis treatment regimens can take up to 15–20 years.[3a] Now, a decade after its approval, trials are still being conducted to establish the place of bedaquiline in the treatment of TB. There are toxicity concerns related to arrythmia, but overall, bedaquiline-containing regimens are effective at treating MDR-TB.[7]

2.1.2 *Pretomanid (Dovprela®)*[8]

The nitroimidazole class of antibiotics (in particular metronidazole) has been used since the 1960s to treat a broad range of infectious diseases and is still widely prescribed today.[9] Recently, Pretomanid was introduced as a part of a combination regimen with bedaquiline and linezolid for the treatment of XDR- or MDR-TB.[8] Two distinct mechanisms are responsible for the antitubercular activity of pretomanid and both pathways require enzymatic reduction of the nitro-group. Under aerobic conditions mycolic acid biosynthesis is inhibited. Under anaerobic conditions the released nitric oxide acts as a respiratory poison.[8] Working

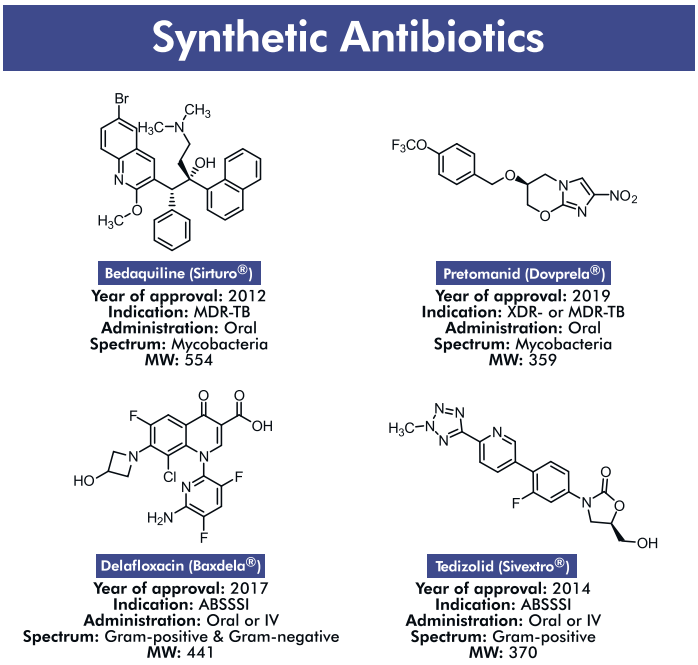

Fig. 1. Synthetic antibiotics. Abbreviations: MDR = multidrug-resistant, XDR = extensively drug-resistant, TB = tuberculosis, ABSSSI = acute bacterial skin and skin structure infections, IV = intravenous.

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with other companies, the TB alliance developed and registered pretomanid for FDA approval.[10] The TB alliance is a not-for-profit product development partnership, and was conceived in 2000 to combat the lack of TB drugs in clinical development.[11] The TB alliance now manages the largest pipeline of new TB drugs.[12] This success highlights that new models for antibiotic development are needed, and can succeed in delivering treatments to the developing world.

2.1.3 *Delafloxacin (Baxdela®)*[13]

Fluoroquinolone antibiotics display broad-spectrum activity and have good oral bioavailability, which make them some of the most commonly prescribed antibiotics.[14] They are binders of the bacterial gyrase and topoisomerase IV enzymes, turning these enzymes into cellular poisons by increasing the number of double-stranded DNA breaks.[14a] Mutations in the target enzymes confer high-level resistance that has become widespread.[14a,15] In contrast to other fluoroquinolones, delafloxacin does not have a strongly basic nitrogen. Therefore, delafloxacin is neutral in acidic environments, which greatly boosts cell permeation and antibacterial activity at low pH. Its balanced activity against the two target enzymes also reduces resistance development.[14b] In many cases, delafloxacin still demonstrated activity against fluoroquinolone-resistant strains.[16]

2.1.4 *Tedizolid (Sivextro®)*[17]

Like the fluoroquinolones, the oxazolidinone class of antibiotics are a rare example of fully synthetic origin. The oxazolidinones inhibit bacterial translation by binding to the P site of the 50S subunit of the ribosome. Two mechanisms of resistance prevail: mutation of the 32S rRNA target and RNA methylation by the methyltransferase *cfr*. As bacteria carry multiple copies of 32S rDNA, target mutation is gradual. Problematically, *cfr*-mediated resistance is horizontally transferable.[18] Tedizolid carries a hydroxy-moiety in place of the acetamide of the first-generation linezolid. While this leads to a slight loss in activity, the reduced size avoids a steric clash with the methylated RNA, overcoming *cfr*-mediated resistance.[19]

2.2 *Natural Product-derived Antibiotics (Fig. 2)*

2.2.1 *Cephalosporins: Ceftaroline fosamil (Teflaro®),*[20] *Cefiderocol (Fetroja®)*[21]

With more than 50 approved drugs, the β-lactam class is one of the most successful among all antibiotics. Next to the penicillins, the carbapenems, and the monobactams, the cephalosporins are important antibacterial agents.[22] In 1945, Giuseppe Brotzu was studying Salmonella contamination of wastewater draining into the sea in Cagliari, Italy. He noticed that people bathing in the seawater were curiously not getting sick. From this water, the fungus *Cephalosporium acremonium* was isolated, marking the discovery of the first cephalosporin.[23] The cephalosporins covalently inhibit the essential penicillin-binding proteins (PBPs) and bacteria fight this by expressing β-lactamases that covalently disarm these antibiotics.[24]

Decades of medicinal chemistry efforts have resulted in five generations of cephalosporins, ever increasing potency and fighting resistance mechanisms.[25] The latest approvals are ceftaroline (as its phosphate prodrug) and cefiderocol.

Like other >4th-generation antibiotics, ceftaroline is permanently zwitterionic, which improves penetration into Gram-negative bacteria, resulting in broad-spectrum activity.[26]

The tradename 'Fetroja®' already hints at an interesting feature of cefiderocol: it contains an iron-binding catechol-moiety. This iron-antibiotic complex is then actively imported by bacterial iron transporters, often referred to as the 'Trojan horse approach'. These advanced structural elements make it a potent candidate to treat multi-drug resistant Gram-negative bacteria.[27]

2.2.2 *Plazomicin (Zemdri®)*[28]

The aminoglycoside class of antibiotics was initially employed with great success, but widespread resistance and serious side effects such as ototoxicity and nephrotoxicity made them fall out of favor.[29] The need for broad-spectrum antibiotics recently rekindled the interest in the aminoglycosides. Like the tetracyclines, the aminoglycosides bind to the 30S ribosomal subunit.[30] A myriad of resistance mechanisms complicates their use and development. Aminoglycoside modifying enzymes (AMEs) are the most prevalent resistance mechanism. These enzymes, among them phosphotransferases, acetyltransferases, and nucleotidyltransferases, covalently disarm aminoglycosides.[29] Plazomicin was designed to minimize vulnerability to AMEs by employing deoxo sugars.[31]

2.2.3 *Tetracyclines: Omadacycline (Nuzyra®),*[32] *Eravacycline (Xerava®),*[33] *Sarecycline (Seysara®)*[34]

In the 1940s, a new antibiotic substance named aureomycin immediately sparked interest with its unprecedented broad-spectrum antibacterial activity. Back then, aureomycin's structure was unknown, until a team of Pfizer scientists and the Woodward group elucidated its structure in 1954.[35] At Pfizer, the C7-chloro substituent was removed using catalytic hydrogenation, yielding a new antibiotic named tetracycline. This marked the discovery of one of the first successful semisynthetic antibiotics.[35a,36] Now, seven decades after their initial discovery, the efforts of countless scientists have culminated in the discovery of third-generation tetracyclines: omadacycline, eravacycline, and sarecycline.

The pioneering work of the Myers group on the total synthesis of tetracyclines, revolutionized tetracycline development. More than 3000 fully synthetic tetracyclines have been synthesized in the Myers lab and at Tetraphase Pharmaceuticals. This was enabled by a convergent synthesis strategy, which has been carried out at multi-kilogram scale.[22,37] Eravacycline is the only tetracycline, and one of the only natural product-derived antibiotics that is manufactured in a fully synthetic fashion.[37,38]

The mechanism of action of tetracyclines has been studied in great detail, and structural work elucidated the details of their binding to the A site of the 30S subunit of the ribosome.[30] To counteract ribosome inhibition, bacteria have developed a range of resistance genes. The main pathways include the expression of protective enzymes, efflux pumps, and enzymes that directly degrade tetracyclines.[39] Omadacycline overcomes several protection and efflux mechanisms.[40] Sarecycline is unique among tetracyclines with its C7 extension that extends into the mRNA channel, which improves binding and helps it overcome resistances.[41] These advances are still threatened by other emerging resistances such as the *tet*(X5) gene, which encodes a FAD-dependent monooxygenase that oxidatively degrades tetracyclines.[42] Strains harboring this gene are resistant to tigecycline, eravacycline, and omadacycline.[43]

2.2.4 *Lefamulin (Xenleta®)*[44]

The pleuromutilins were discovered in 1951, yet it took 68 years until the first systemic pleuromutilin antibiotic was approved for human use. Nabriva Therapeutics AG synthesized and evaluated more than 1200 derivatives to identify lefamulin as a clinical candidate. Extensive variation of the side-chain showed that it had little influence on target activity, but that it was crucial in dictating the toxicity profile and required oral dose.[45] Despite this success, Nabriva announced in January 2023 that they were winding down operations and seeking to out-license lefamulin, highlighting how difficult it is to remain profitable in the antibiotics sector.[46]

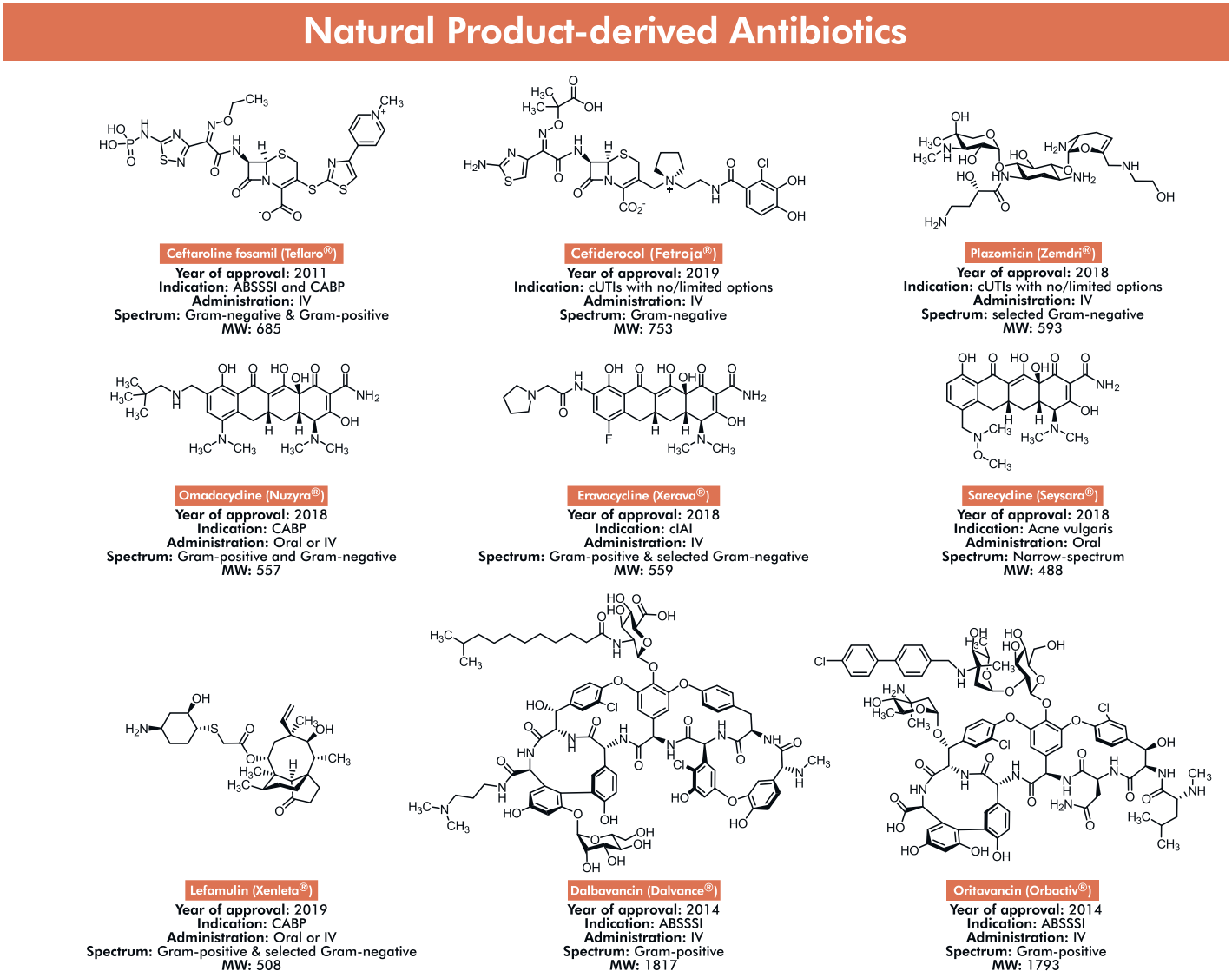


Fig. 2. Natural product-derived antibiotics. Abbreviations: ABSSSI = acute bacterial skin and skin structure infections, CABP = community-acquired bacterial pneumonia, IV = intravenous, cUTIs = complicated urinary tract infections, cIAI = complicated intra-abdominal infections.

2.2.5 *Lipoglycopeptides: Dalbavancin (Dalvance®),*[47] *Oritavancin (Orbactiv®)*[48]

Depending on their substitution patterns, antibiotics of this class are considered glycopeptides, lipopeptides, or glycolipopeptides. There are two main families: the vancomycin family and the teicoplanin family whose members have an additional ether-bridged macrocycle. Dalbavancin was derived from the teicoplanin A40926, and oritavancin was derived from chloroeremomycin of the vancomycin family.[49] These antibiotics have complex mechanisms of action that are still under investigation. Their primary function is to bind the D-Ala-D-Ala motif of the peptidoglycan, preventing construction and cross-linking of this cellular layer. It took three decades for resistance to this class to emerge in the clinic. A complex signaling cascade of five proteins is required to reprogram the cells to incorporate a D-Ala-D-lactate instead, which leads to vancomycin resistance.[49a]

The second-generation lipoglycopeptide dalbavancin is able to overcome VanB, but not VanA, resistance. Cell-membrane anchoring *via* its lipid tail further increases potency. Isolates that are resistant to dalbavancin, but susceptible to vancomycin, have been observed in the clinic, suggesting that there are new, lipoglycopeptide-specific resistance mechanisms.[49a,50]

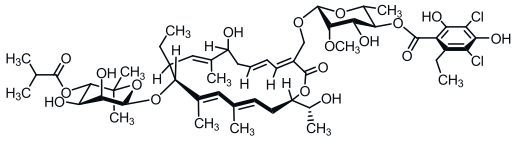
Oritavancin includes a chlorobiphenyl-moiety that facilitates dimerization and membrane anchoring. Oritavancin has been shown to act through several distinct mechanisms: inhibition of transglycosylation, inhibition of transpeptidation, and disruption of cell membrane integrity. *In vitro* resistance to oritavancin has been observed, but fortunately no resistant strains have been observed in the clinic to date.[49a,b,50a,51]

2.3 *Natural Product Antibiotics (Fig. 3)*

2.3.1 *Fidaxomicin (Dificid®)*[52]

As the first member of its new class, RNA polymerase inhibitor fidaxomicin was discovered in 1972, yet only approved for clinical use in 2011.[53] Fidaxomicin was shown to be superior to vancomycin, the previous standard of care in the treatment of *Clostridioides difficile*-associated diarrhea (CDAD).[52,54] The fact that fidaxomicin is almost fully confined to the gastrointestinal tract results in little toxicity. While low systemic absorption is desirable for the treatment of CDAD, it prevents the use of fidaxomicins as a treatment for TB, despite good *in vitro* activity. To expand the spectrum of fidaxomicins and to counter emerging resistance new semisynthetic derivatives are required, which is an ongoing effort in our group.[55]

Natural Products



Fidaxomicin (Dificid®)
Year of approval: 2011
Indication: CDAD
Administration: Oral
Spectrum: Narrow-spectrum
MW: 1058

Fig. 3. Natural product antibiotic. Abbreviations: CDAD = *Clostridioides difficile*-associated diarrhea.

3. Conclusion

In this review, we present an overview of the fourteen small-molecule new molecular entities approved for the treatment of bacterial infections in the time frame 2010–2022.[56] Decades of medicinal chemistry efforts around the globe came to fruition with these next-generation antibiotics and their discovery was enabled and driven by innovation in chemical synthesis. Continued investment in the fascinating chemistry and biology of natural product-inspired and synthetic antibiotics is thus warranted.

Acknowledgements

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