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Advances in macrocyclic peptide-based antibiotics

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ABSTRACT

Macrocyclic peptide-based natural products have provided powerful new antibiotic drugs, drug candidates, and scaffolds for medicinal chemists as a source of inspiration to design novel antibiotics. While most of those natural products are active mainly against Gram-positive pathogens, novel macrocyclic peptide-based compounds have recently been described, which exhibit potent and specific activity against some of the most problematic Gram-negative ESKAPE pathogens. This mini-review gives an up-date on recent developments.

1. Introduction

The global emergence of multi-drug resistant pathogens has placed a severe strain on health care systems world-wide. Since the first alarming reports by the Infectious Disease Society of America (IDSA, "Bad bugs, no drugs, no ESKAPE"),[1] there has been an impressive shift in public and government awareness for the potential threat imposed by a global antibiotic crisis.[2,3] Several initiatives have been launched with the aim to improve: sanitation and prevention of the global spread of infections, implementation of a global surveillance system for monitoring drug resistance, avoid unnecessary over-use of antimicrobials,[4,5] and foster drug discovery and development of novel antibiotics by increasing both public and private funding opportunities.[4]

In a most recent WHO report[5] a global priority pathogens list (PPL) of antibiotic resistant bacteria has been established to guide the prioritization of funding and incentives for discovery and development of new and effective antibiotic treatments. It is clear that there is an urgent need for novel classes of antibiotics with preferentially novel mechanisms of action to complement our arsenal of current drugs, particularly against Gram-negative ESKAPE pathogens such as carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacter* spp.[5]

2. Antibiotic drug discovery approaches

Traditionally, novel antibiotics were largely discovered by phenotypic screening approaches of various sources of compounds, such as natural products isolated from extracts of soil microbes and semi-synthetic or fully synthetic compound libraries derived from known antibiotics. To date, target-based *in vitro* screening approaches have been clearly less successful.[6] However, recently novel approaches have been described that link phenotypical screening with target-centric chemical genomics.[7] Other approaches investigate e.g. untapped natural product sources such as uncultured bacteria for discovering new antibiotics combining high-throughput genome sequencing with high throughput microbial cultivation and synthetic biology.[8,9] This strategy may be especially valuable since it has been estimated that so far less than 1% of all environmental microbes have been cultured in laboratory settings.[9]

So far, natural product-screening has undoubtedly been the most productive source for discovering new antibiotics as exemplified by the discovery of the penicillins, cephalosporins, the macrolides such as erythromycin, the glycopeptides such as vancomycin and teicoplanin, the tetracyclines and the aminoglycosides.[9,10] Among antibiotic scaffolds that have emerged recently from natural products, macrocyclic peptides and depsipeptides seem particularly privileged.[11–15]

This mini-review will focus mainly on macrocyclic peptide-based scaffolds that led to the discovery of preclinical and clinical stage antibiotics and/or marketed drugs. The vast literature relating to antimicrobial peptides in general has been reviewed elsewhere.[16,17] It is noteworthy, that there are significantly less

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scaffolds (macrocyclic and non-cyclic) active against Gram-negative bacteria. Lack of membrane permeation of many lipophilic compounds, particularly through the highly negatively charged outer-membrane (OM), seems to be the main problem. In addition, Gram-negative bacteria have efficient efflux pumps and resistance mechanisms.[15] In recent years antibiotics have been discovered that target specifically outer-membrane proteins (OMP's) in Gram-negative bacteria.[15]

3. Macrocyclic peptide-based antibiotics against Gram-positive bacteria

Table 1 summarizes macrocyclic peptide-based antibiotics classified in compounds that are active mainly on Gram-positive (part 1), both Gram-negative and Gram-positive (part 2), and Gram-negative (part 3) pathogens.

3.1. Macrocyclic glycopeptide antibiotics

Glycopeptides of the vancomycin-teicoplanin family (Table 1, Fig. 1a) have been in clinical use for many years.[3,10,11] They are widely used as antibiotics against Gram-positive bacteria and as last resort antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin and analogues bind to the D-Ala-D-Ala portion of lipid II and as a result inhibit peptidoglycan biosynthesis. Spurred by the emergence of vancomycin-resistant *Enterococcus* (VRE) and MRSA, new analogues of the vancomycin-teicoplanin family have reached the market. Dalbavancin (Dalvance, Xydalba, Table 1)[3] got FDA approval in 2014 for acute bacterial skin and skin structure infections (ABSSSi) and is characterized by an unusually long half-life (6–10 days) as a result of high protein binding.[11] Oritavancin (**1**, Orbactiv, Fig. 1a) and telavancin (**2**, Vibactiv, Fig. 1a) are additional semi-synthetic glycopeptide analogues which got FDA approval in 2014 and 2009, respectively, for the treatment of complicated skin and skin structure infections (cSSSi). Telavancin **2** got additional FDA approval in 2013 for treatment of hospitalized patients with bacterial pneumonia and in 2016 an expanded label. Cefilavancin (**3**, Fig. 1a) is a cephalosporin-glycopeptide heterodimeric conjugate that was undergoing a Phase III trial as a treatment of Gram-positive complicated skin and skin structure infections in 2016, whereas TD-1607 (**4**, Fig. 1a), which is another cephalosporin-glycopeptide heterodimeric conjugate with different connectivities, entered Phase I trial in 2013. Both compounds **3**, and **4** belong to a well-documented approach to covalently connect two different antibiotics[3] with different mechanisms of action.

3.2. Macrocyclic lipopeptide antibiotics

Daptomycin (**5**, Cubicin, Fig. 1a) was approved by the FDA in 2003 and is used to treat life-threatening Gram-positive infections.[10,11] The main mechanism of action of daptomycin is Ca^{2+}-mediated disruption of membrane function.[36] Surotomycin (**6**, MK-4261, Fig. 1a), a semi-synthetic analogue of daptomycin completed Phase III trials in 2015 for the treatment of *Clostridium difficile* infections (CDI)[3] where it showed improved efficacy over daptomycin, however, was discontinued later (Merck, annual report 2015). Whereas daptomycin is intrinsically inactive against Gram-negative bacteria due to lack of OM permeation, daptomycin-siderophore conjugate **7** (Fig. 1a) was designed in an attempt to overcome this hurdle by using the siderophore moiety for actively transporting **7** through the OM ("Trojan horse approach")[18] of Gram-negative bacteria. As a result, analogue **7** shows promising activity against *Acinetobacter baumannii*, including multi-drug resistant isolates, *in vitro* and *in vivo*,[18] however, was not active against e.g. *Pseudomonas aeruginosa*. The clinical success of daptomycin after a long and cumbersome

Table 1
Overview on macrocyclic peptide-based antibiotics.

Natural macrocyclic peptides	Synthetic/semi-synthetic derivatives	MoA/target
1) Antibiotics against mainly Gram-positive bacteria		
Vancomycin/Teicoplanin	Dalbavancin[3], Oritavancin (1); Telavancin (2)[10,11]; Cefilavancin (3); TD-1607 (4)[3]	Peptidoglycan biosynthesis[8]
Ramoplanin[11]		Binds to lipid II
Daptomycin (5)	Surotomycin (6)[10]; cpd 11 (7)[18]	Membrane depolarization
WAP-8294A2[11]		Binds to membrane phospholipids
Lysobactin; katanosin[11,13]		Inhibits cell wall biosynthesis
Biphenomycins[9]		Inhibition of protein biosynthesis
Streptogramins A/B[11,13]	Etamycin A (8)[19]	Inhibition of protein biosynthesis
Teixobactin (9)[20]	Synthetic analogues[21]	Binds to lipid II/III
Mannopeptimycins[9,22]		Binds to lipid II
GE2270A (10)[11]	CB-06-01 (11)[10]; kocurin (12)[19]	Inhibition of elongation factor TU (EF-TU)
Nisin[10,16]		Binds to Lipid II (pyrophosphate)
Defensins[16,17]	Plectasin[3]	Binds to Lipid II
2) Antibiotics against Gram-positive/Gram-negative bacteria		
Arylomycins[3,10]	Actinocarbasin (13)[10]; M131(14)[3,10]	Signal peptidase type I[23]
Krysinomycin (15)[11,14,15]		Signal peptidase I
Globomycin (16)[10,14,15]	Synthetic analogue (17)[24]	Signal peptidase II[23]
ADEP's: Enopeptins (18)[11,13]	ADEP 4 (19)[25]	ClpP[23]
Lassomycin[9,26]		ClpC1
Protegrin I, tachyplesin I[11]	IB-367 (20)[27]	Membrane lysis
Griselimycin[9,28]		DnaN[28]
3) Antibiotics against mainly Gram-negative bacteria		
Polymyxins (21); colistin (22)[11,15,29]	Colistin methanesulfonate (23); FADDI-002 (24)[29]	Membrane depolarization
Octapeptins (25)[12,29]	Octapeptin B5 (Battacin) (26)[12,29]	Membrane depolarization
Argyrins A-H (27)[30,31]		Elongation Factor G (EF-G)
Protegin-I	PEM: L27-11, POL7001 (28)[32] Murepavadin (POL7080) (29)[33]	OMPTA class: Inhibition of LptD/E (LPS translocation)
Protegin-I	JB-95 (PEM);[34] 30 (PEM)[35]	OMPTA class (LPS/OMPs)