streptogramins are bacteriostatic individually but bactericidal and synergistic when combined (see Synercid; Table 23.3). Efforts are in progress to evaluate new orally active streptogramins since synercid is not orally available and is administered intravenously.

23.7.2.6 Oxazolidinones

Members of this class (discovered in the mid-1980s) have a common oxazolidinone core with various N-linked aryl and heterocyclic rings and short C(5) side chains. Despite displaying bacteriostatic activity against Gram$^+$ pathogens, they were not pursued due to toxicity. Subsequent efforts by Pharmacia led to the antibiotic Linezolid (Figure 23.7) approved by the FDA (2000) for hard-to-treat Gram$^+$ bacterial infections (e.g., vancomycin-resistant enterococci).

Widespread resistance was not common to this class, probably due to the lack of such structures in nature. Prolonged therapy with linezolid has been linked to rare instances of lactic acidosis and liver injury. Continued efforts have focused on improving its spectrum, solubility, and pharmacological and toxicity profiles. Second-generation oxazolidinones are currently undergoing clinical trials.

23.7.2.7 Pleuromutilins

Pleuromutilins have a common fused cyclo-octane/pentanone with a bridged cyclohexane ring (Figure 23.7). Pleuromutilins, (1950s; *Pleurotus mutilis*), were used extensively in veterinary medicine. Ritapamulin (FDA approved, 2007), a semisynthetic pleuromutilin active against Gram$^+$ *S. aureus* and *S. pyrogens*, is used topically.

23.8 NEW DEVELOPMENTS IN ANTIBACTERIAL RESEARCH

Current antibiotic research is a massive line of work backed by advances in molecular structure determination, structure-based design, chemical synthesis, screening strategies, and genomic data, to mention a few. Given the breadth of the field, we confine our discussion to only a couple of interesting examples.

In clinical pipeline are new derivatives/molecules to address issues such as resistance, host toxicity, Gram-negative pathogens. Among the new molecules is POL7080 (Polyphlor Ltd., Basel, Switzerland; completed phase I clinical trials) which acts on an unconventional target LptD—an essential outermembrane protein, involved in exporting lipopolysaccharide molecules across the periplasm. POL7080 is a peptidomimetic molecule with potent antibacterial activity against *P. aeruginosa*. It has chemically evolved from a natural product, Protegrin I, an antimicrobial peptide from porcine leukocyte. Protegrin I disrupts the membrane via pore formation and has little clinical utility due to significant hemolytic activity.

One of the factors hampering natural product antibiotic discovery is that only a small minority of bacteria are cultivable in the lab. Uncultured bacteria accounts for approximately 99% of all species in external environments. Lewis K. and coworkers developed a novel method for growing uncultured bacteria which led to the discovery of the antibiotic Teixobactin (2015). It inhibits cell wall synthesis by binding to a highly conserved motif of lipid II (precursor of peptidoglycan) and lipid III (precursor of cell wall teichoic acid). Teixobactin (currently in preclinical stage) is potent against Gram$^+$ pathogens including *M. tuberculosis* with no detectable resistance.

23.9 CONCLUDING REMARKS

Development of antibiotics, one of the oldest fields in medicinal chemistry, continues to have a huge impact on human health, saving innumerable lives. This research domain was neglected during the last three decades, leaving a lean clinical pipeline and many difficult-to-treat bacterial infections. There is a pressing need for new antibiotics. The recent revival of interest in antibiotic research in some pharmaceutical companies and public–private partnerships will hopefully reverse the downward trend.