(ciprofloxacin, moxifloxacin), tetracyclines (doxycycline, minocycline, tigecycline), NOV, chloramphenicol, fosfomycin and others except aminoglycosides, and carbapenems. Frequently, the observed effect was limited to *P. aeruginosa* except in the case of RIF where the potentiating effects were seen across most MDR GNB including *E. coli*, *K. pneumoniae*, *A. baumannii*, and *Enterobacter cloacae*. Moreover, a few polybasic antimicrobial peptides have shown to synergize RIF. For instance, the cationic antimicrobial peptides magainin II and cecropin A showed a synergistic fractional inhibitory concentration index (FICI) = 0.31 with RIF in the wild-type *P. aeruginosa* strain ATCC 27852. Moreover both peptides reduced the bacterial count in blood of wild-type and MDR *P. aeruginosa*-infected rats as well as mortality when treated with a combination of RIF and magainin II or cecropin A (Cirioni et al. 2008). Recently, short polybasic proline-rich lipopeptides (Domalaon et al. 2018d) and also ultrashort cationic di-lipopeptides (Domalaon et al. 2018b) have been shown to synergize RIF and minocycline against MDR *P. aeruginosa* isolates.

18.12 Repurposing of Antibiotics as Potent Agents Against MDR GNB

Besides polymyxin and TOB-based adjuvants, other adjuvants have been identified to enhance the antibacterial effects of antibiotics. Among them, two FDA-approved drugs pentamidine and loperamide (Figure 18.6) with no antibacterial applications stand out. The antiprotozoal drug and outer membrane permeabilizer pentamidine displayed synergy with antibiotics typically restricted to Gram-positive bacteria, yielding effective drug combinations with activity against a wide range of Gram-negative pathogens except *P. aeruginosa in vitro* and against systemic *A. baumannii* infections in mice (Stokes et al. 2017). Similarly, loperamide (an antidiarrheal agent) sensitized the tetracycline antibiotics to MDR GNB via a decrease in the electrical component of the proton motive force, resulting in increased pH gradient across the inner membrane (Ejim et al. 2011). The ΔpH would in turn increase uptake of tetracycline antibiotics, thereby overcoming intrinsic resistance. Finally, triclosan is a

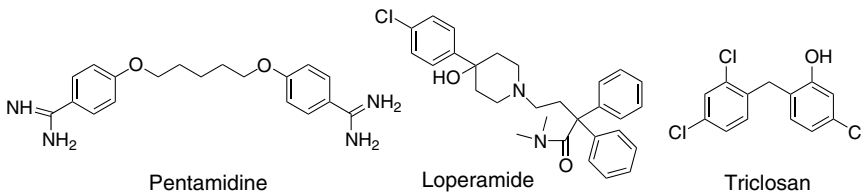

Figure 18.6 Structure of non-polymyxin or non-tobramycin-based antibiotic adjuvants that potentiate antibiotics against GNB.