

resistance through bacterial populations (Nakamura et al. 2004). More often than not, resistance induced by an antibiotic leads to decrease of efficacy of other structurally unrelated antibiotics, resulting in the development of multidrug-resistant (MDR) bacterial strains. The specter of untreatable infections is becoming a real threat as the resistance was recently observed against the drugs of last resort, such as vancomycin and colistin (Boucher et al. 2009; Liu et al. 2016), and the demand for new antibiotic therapies is critical.

In the era of the antibiotic resistance, the development of the new antibiotics focuses on the new or unexplored targets present in resistant strains, while the alternative strategies include developing agents that target the mechanisms responsible for antibiotic resistance and failure of infection treatments

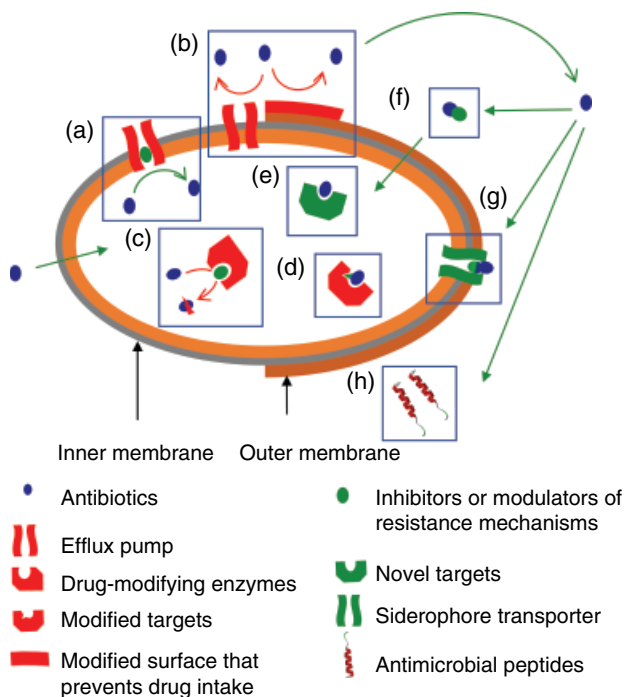


Figure 13.1 Schematic representation of the mechanisms of resistance in Gram-positive and Gram-negative bacteria and approaches for the design of therapeutic agents to overcome resistance. (a) Resistance by efflux and design of efflux pump inhibitors (EPI). (b) Resistance by preventing influx through the bacterial surface modification or porin downregulation. (c) Design of inhibitors of drug-modifying enzymes. (d) Design of drug analogues to inhibit modified targets. (e) Design of antibiotics against novel targets or with novel mechanism of action. (f) Drug complexation or conjugation. (g) Drug influx increase through siderophore receptors. (h) Use of antimicrobial peptides (AMP).