



Figure 18.4 Structure of hydrophobic antibiotics with large molecular weight that display poor antipseudomonal properties.

type are vaguely defined as hydrophobic antibiotics with an MW above 600 g mol^{-1} . The polybasic molecule that enhances outer membrane uptake is called a permeabilizer or adjuvant. Several hydrophobic antibiotics with an MW above 600 Da possess selective and potent activity against Gram-positive bacilli but poor antibacterial activity against GNB. Among others these include the RNA polymerase inhibitor rifampicin (RIF) (Calvori et al. 1965), the aminocoumarin antibiotic novobiocin (NOV) that inhibits the GyrB subunit of DNA gyrase at a different site than fluoroquinolones (Biacchi and Manchester 2015) and vancomycin that inhibits the cross-linking of the peptidoglycan chains (Figure 18.4) Levine (1987).

18.11 Repurposing of Hydrophobic Antibiotics with Large Molecular Weight and Other Antibacterials as Antipseudomonal Agents Using Polybasic Adjuvants

RIF has a broad spectrum of activity including Gram-positive bacteria and certain GNB, although it is not recommended as a single therapeutic agent because of rapid emergence of resistance *in vitro* and *in vivo* (Song et al. 2008). Apart from its use against *Staphylococcus aureus* infections, RIF has been used in triple combination therapy against infections caused by *Mycobacterium tuberculosis* as well as in combination with polymyxins against CR-GNB, most notably against *A. baumannii* (Bassetti et al. 2008). The use against *A. baumannii* is based on preclinical studies indicating synergism, but this effect has not been corroborated by clinical evidence of benefit based on recent clinical trials.