nonproducing bacteria. Other phylogenetic analyses involving, for example, β-lactamases also showed the ancient independent evolution of the corresponding genes in antibiotic-producing and nonproducing microbiota (Ogawara 1993; Hall and Barlow 2003). Thus, the original antibiotic resistance gene pool was supposedly more widespread and existed in many other bacteria other than antibiotic producers.

23.7 Second-Generation Tetracyclines

The rapid emergence and dissemination of tetracycline resistance among the bacterial pathogens incited the development of the second-generation tetracyclines such as minocycline, which became available in 1966 (Redin 1966), and doxycycline, which became available in 1967 (Corey 2013). Essential for the development of these semisynthetic tetracyclines was the establishment of the chemical structure of natural tetracyclines (Nelson and Levy 2011). They are still used to treat many different infectious diseases, such as urinary and intestinal tract infections, respiratory infections, skin infections, acne, gonorrhea, tick fever, chlamydia, eye infections, periodontitis, and others. Besides the antibacterial effects, they also display other potent activities directed toward the eukaryotic cell targets (Aminov 2013b). In particular, minocycline displays strong anti-inflammatory, neuroprotective, anti-proteolytic, and anti-apoptotic properties, as well as inhibiting angiogenesis and metastatic growth (Garrido-Mesa et al. 2013). In addition, it displays antioxidant activity, inhibits several enzyme activities, and modulates immune cell activation and proliferation (Aminov 2013b). Thus, the applications of the second-generation tetracyclines could be potentially extended to other than antimicrobial use.

23.8 Third-Generation Tetracyclines

The first representative of the third-generation of tetracyclines, tigecycline (the minocycline derivative 9-tert-butylglycylamido-minocycline, GAR-936), was approved for clinical use by the FDA in 2005. In preclinical studies, tigecycline displayed good activity against tetracycline-resistant strains carrying genes encoding tetracycline efflux determinants (*tet*(A), *tet*(B), *tet*(C), *tet*(D), and *tet*(K)) as well as a gene encoding a ribosomal protection protein (*tet*(M)) (Petersen et al. 1999). Other studies confirmed its efficiency against clinical isolates of *Acinetobacter* spp. including *Acinetobacter baumannii* (Henwood et al. 2002), nontuberculous mycobacteria (Wallace et al. 2002), *Enterococcus* spp. including vancomycin-resistant enterococci (Mercier et al. 2002; Lefort et al. 2003; Nannini et al. 2003), *Staphylococcus aureus* including methicillin-resistant (MRSA) and glycopeptide-intermediate resistant strains (Mercier et al.