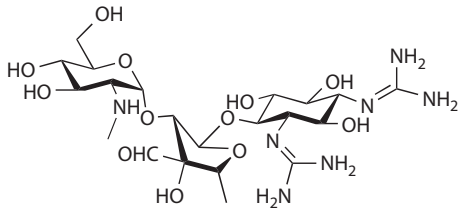
### 23.7.1.2 Tetracyclines

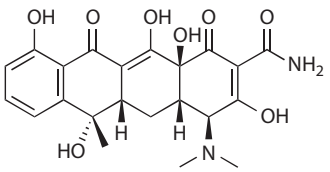
They derive their name from the tetracyclic ring system which is octahydronaphthacene. The first tetracyclines were chlortetracycline (1948; *Streptomyces aureofaciens*) and oxytetracycline (1950; *Streptomyces rimosus*). The structure was published in 1952 but complete stereochemistry was obtained later from X-ray diffraction analysis. These studies revealed that the removal of chlorine from chlortetracycline by hydrogenolysis led to an active product, tetracycline (Figure 23.7). Tetracycline was also obtained by fermentation of a medium poor in chloride using appropriate strains, e.g., *S. alboniger, S. viridifaciens*, etc.

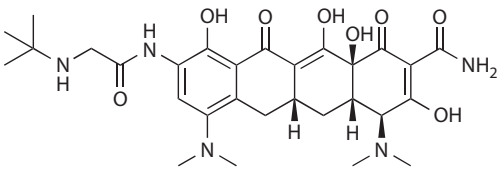
*Semisynthetic tetracyclines*: Chemical manipulations of oxytetracycline led to the production of metacycline. Hydrogenation of metacycline under suitable conditions gave doxycycline (II generation). Doxycycline is very stable (no C6–OH group) and is lipophilic. It is more completely absorbed after oral administration. Minocycline (1972) is prepared by the chemical treatment of 6-deoxy-6-demethyltetracycline.

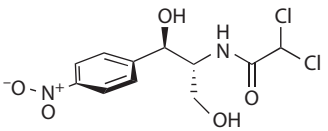
The tetracycline binding site in both prokaryotes and eukaryotes is structurally conserved. If not for the ability of bacteria to accumulate tetracyclines far more efficiently than mammalian cells, the drug does not differentiate between the eukaryotic and prokaryotic ribosomes. They are bacteriostatic, truly broad-spectrum antibiotics with low incidence of side effects which explains their position as first-line antibiotics.

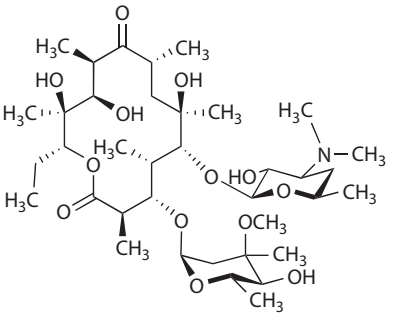
*Glycylcyclines* have *N*,*N*-dimethylglycylamido moiety on the C9 position of ring D. Tigecycline (1998) (Figure 23.7), a glycyl derivative of minocycline, was approved 30 years after the last member from the tetracycline class. The modification resulted in broader spectrum of activity.



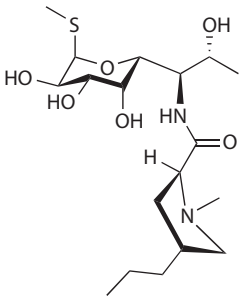




**FIGURE 23.7** Representative structures of antibiotics affecting protein biosynthesis. (*Continued*)