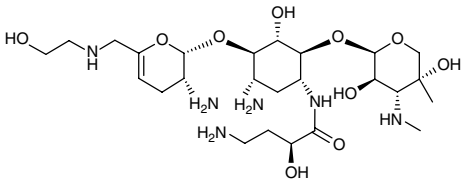

40; Plazomicin

14.6 Early Tetracyclines: Aureomycin and Terramycin

In 1948, Duggar reported the discovery of aureomycin, subsequently identified as chlortetracycline (**41**) by Woodward's group, who also identified terramycin as oxytetracycline (**42**). The early history of the tetracyclines was covered in an excellent article in 2001 by Nelson (2001) in the book *Tetracyclines in Biology, Chemistry and Medicine,* also edited by Nelson. Another chapter in this book by Schneider (2001) discussed the metal-binding characteristics of tetracyclines, a discussion that has become relevant in the last few years.

What is also of significant interest is that the tetracycline nucleus was probably the first drug "structure" that led to the identification of "active transport" as a mechanism of removal of a drug from its target, in addition to "ribosome protection." A very recent discussion of the various mechanisms has been published by Markley and Wencewicz (2018), which should be consulted to demonstrate the many interlocking systems that bacteria use to defend themselves against this class of molecules. Another interesting review, in a journal that few microbiologists would probably read, is the discussion by Guerra et al. (2016) in *Coordination Chemistry Reviews*, where they demonstrate that using a platinum or palladium complex with tetracycline can overcome the *tetX* and other transporters, leading to abrogation of the resistance in microbes resistant to tetracyclines (Guerra et al. 2016).

14.6.1 Semisynthetic Tetracyclines from 2005

Based on the previous sections and, in particular, the resistance profiles that have arisen since the late 1940s, one might think that this particular base structure is not one to continue to study for new antibiotics. However, in 2005 Lederle (Wyeth and then Pfizer) had tigecycline (**43**) approved by the FDA. This is effectively a derivative of the slightly modified tetracycline, minocycline (**44**), and is a "glycylcycline." The original and subsequent papers covering this compound are worth reading as what was effectively a relatively simple modification, led to a new and active tetracycline (Sum et al. 1993; Petersen et al. 1999; Hunter and Castaner 2001).