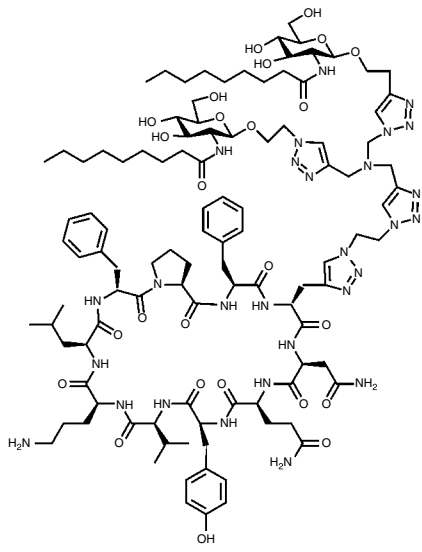
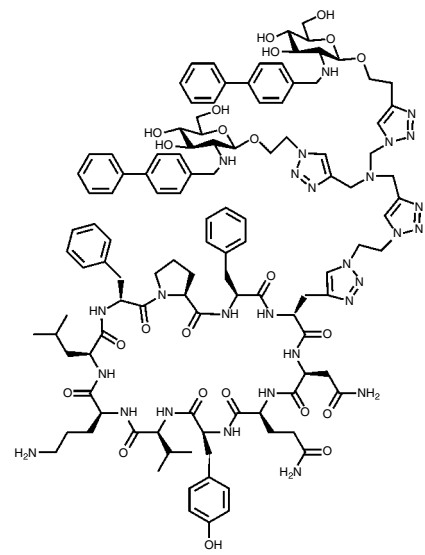
destruction or modification of compounds (Wright 2005; Chellat et al. 2016). Inspired by these explored antibiotic resistance mechanisms, more and more researchers have been beginning to target modification on existing antibiotics and have obtained many exciting achievements.

For improving the binding ability between antibiotics and cell walls, the bactericidal compounds (**21**) and (**22**) were synthesized by Walsh (Lin and Walsh 2004). In this work, the carbohydrate was utilized for modifying the core structure of tyrocidine, which was a kind of nonribosomal peptide without specific target. The antibacterial and hemolytic assays demonstrated that the obtained Tyc4pg-14 and Tyc4pg-15 had improved the therapeutic index, compared with the natural tyrocidine (Scheme 16.7).

In order to realize the purpose of targeted modification, Sanjeev Mariathasan et al. used anti-*S. aureus* antibody to covalently link with highly efficacious antibiotics and improved the binding ability and targeting of the selected antibacterial drugs (Scheme 16.8) (Lehar et al. 2015). By further introducing the intracellular protease-sensitive linker, the novel antibody–antibiotic conjugate could be activated only by the phagolysosomal protease, and the released active group could efficiently eliminate intracellular *S. aureus*. A virulent subset of *S. aureus* was selected as the model pathogens, because it could establish intracellular infection even in the presence of vancomycin. After treated with these model bacteria, it was confirmed that the antibody–antibiotic conjugate



21 Tyc 4PG-14



22 Tyc4PG-15

Scheme 16.7 Chemical structures of (**21**) and (**22**).