14.3.6 Glycopeptides

14.3.6.1 Vancomycin and Chemical Relatives

The antibiotics based on peptides that have had the longest "continuous usage," are those in the vancomycin class, normally known as GPAs. Vancomycin (**20**) was first introduced into medicine in the middle to late 1950s by Lilly (Griffith 1981). Although in clinical use for over 20 years, it was not until 1982 that the full structure was identified when Harris and Harris correctly identified an asparagine residue in the antibiotic (Harris and Harris 1982). Subsequently, this molecule was used mainly as a "treatment of last resort" when resistance to methicillin in *Staphylococcus aureus* arose, giving rise in due course to the soubriquet MRSA for this resistant organism. Relatively recently, in order to help overcome the side effects of the normal IV administration of vancomycin, Shire Pharmaceuticals marketed an oral formulation "Vancocin Pulvules®." This can be considered a product of "pharmaceutics manipulation of its physical properties" in order to produce an orally active compound, but it does not alter the basic structure of the molecule itself.

As with all antibiotics, resistance to vancomycin developed, and for a considerable amount of time, the reason for this resistance was not known. Vancomycin and similar molecules predominately function as antibiotics by binding to the L-Lys-D-Ala-D-Ala-COOH terminals of the cross-links in the Gram-positive cell wall. In the late 1970s, the author (and colleagues) then at Smith, Kline & French (SK&F) devised a very simple screen for discovering vancomycin-like glycopeptides, by initially competing their activity on a simple disc assay on a test plate of the well-known *S. aureus* strain 209P. They used a sacculus preparation from the Gram-positive bacterium *Bacillus subtilis*, as the cost at that time of acetyl-L-Lys-D-Ala-D-Ala-COOH was prohibitive. This was published in addition to using the tripeptide method, many years later as SK&F ceased antibacterial discovery in 1985 (Rake et al. 1986). This resulted in the discovery and then subsequent development of the aridicins (Shearer et al. 1985). Subsequent work demonstrated that the *VanR* phenotype was simply due to a change in the terminal D-Ala residue to D-Lactate in the *vanA, vanB,* and *vanD* or to D-Ser in the *vanC, vanE*, and *vanG* phenotypes.

The rise of the vancomycin-resistance phenotype in clinical practice, was such that new antibiotics were required to deal with it, as one now had an increase in infections where MRSA was also exhibiting resistance to vancomycin. The D-Lac modification increased resistance by roughly 1000-fold, with