4.6.4 Incorporation of Metal Chelating Moiety to Vancomycin to Impart New Mechanism of Action

The pyrophosphate of the bacterial cell wall is necessary for the transfer of cell wall precursors from the cytoplasm to the outer side. In a report, vancomycin was conjugated to a Zn^{2+} binding ligand (Figure 4.7) to overcome vancomycin resistance (Yarlagadda et al. 2016c). The dipicolyl amine moiety is known to capture the divalent zinc ion with high selectivity. Thus, this dipicolyl–vancomycin conjugate (**22**) forms a complex with the pyrophosphate groups of cell wall lipids in addition to binding to the cell wall precursor peptides. A 375-fold (MIC = 2 μM) higher *in vitro* activity than vancomycin against VRE and enhanced cell wall biosynthesis inhibition was achieved by this design. This compound was found to reduce the bacterial load in VRE kidney infection model by 5 log CFU ml^{-1} as compared with the untreated control. Further, the compound did not induce resistance in MRSA.

4.7 Glycopeptides Under Clinical Trials

There are currently two glycopeptide derivatives under clinical trials (Figure 4.8). These are vancomycin–cephalosporin hybrids developed by Theravance Biopharma Inc. – cefilavancin (**23**) and TD-1607 (**24**) are currently

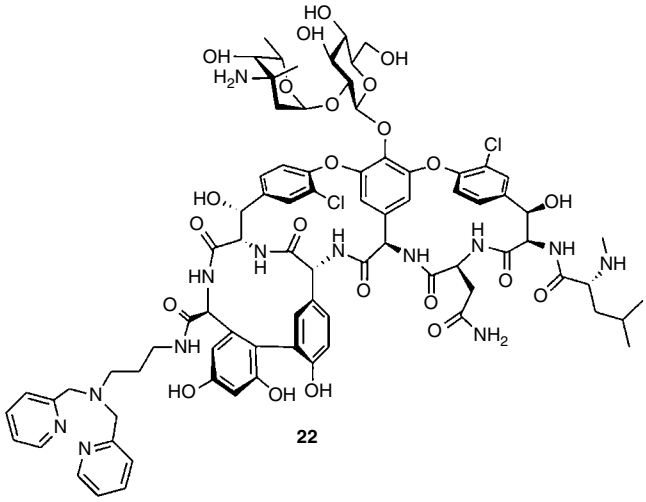

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Figure 4.7 Vancomycin–dipicolyl derivative that interacts with the pyrophosphates of bacterial membrane.