(Xie et al. 2011, 2012). Upon replacement with sulfur, the binding affinity to D-Ala-D-Ala and D-Ala-D-Lac was reduced due to the larger size of sulfur. The [Ψ[C(=NH)NH]Tpg^4]vancomycin aglycon (**6**), with an amidine in place of the carbonyl at residue 4 of vancomycin aglycon, binds to both the unaltered peptidoglycan terminal D-Ala-D-Ala and the mutated ligand D-Ala-D-Lac due to its ability to serve as a hydrogen bond donor or acceptor (Xie et al. 2011). This amidine derivative of vancomycin aglycon displayed an MIC of less than 0.5 μg ml^{-1} against sensitive and resistant bacteria. Later, Boger et al. developed appended a (4-chlorobiphenyl)methyl moiety to the vancosamine moiety of [Ψ[C(=NH)NH]Tpg^4]vancomycin (**7**) to incorporate both enhanced binding affinity and favorable hydrophobicity within the same molecule (Okano et al. 2014). This resulted in high activity against vancomycin-resistant bacteria with MICs in the range of 0.005–0.06 μg ml^{-1}.

4.6.1.2 Attachment of H-Bond-Forming Moieties

It was observed that a water molecule bridged the carboxylic group of vancomycin and the ligand in the crystal of vancomycin–ligand complex (Nitanai et al. 2009). This indicated that modification of the C-terminus with moieties that can form hydrogen bonds with the target peptide could enhance binding affinity. Various cyclic and acyclic sugars such as maltose, lactobionic acid, gluconic acid, and cellobiose were conjugated to vancomycin to increase the binding affinity to the mutated target peptide (D-Ala-D-Lac) (Yarlagadda et al. 2015a). The binding affinity of these sugar–vancomycin conjugates was comparable to that of vancomycin. The association constant (K_a) of vancomycin was found to be 1.1×10^5 M^{-1} and 5×10^2 M^{-1} to D-Ala-D-Ala and mutated terminal, D-Ala-D-Lac, respectively. The derivative in which lactobionic acid was conjugated to the carboxylic acid group of vancomycin (**8**, Figure 4.3) exhibited approximately 150-fold ($K_a = 8.8 \times 10^4$ M^{-1}) higher affinity for *N,N′*-diacetyl-Lys-D-Ala-D-Lac as compared with vancomycin. An improved antibacterial activity leads to an MIC of 36 μM against VRE (VanA phenotype), as opposed to 750 μM against vancomycin. To further enhance the activity against vancomycin-resistant strains, alkyl chains (octyl to dodecyl) were conjugated to the amino group of vancosamine of compound to yield the lipophilic vancomycin–sugar conjugates. This was expected to impart additional membrane-anchoring properties. The lead molecule (**9**) bearing decyl alkyl chain at the vancosamine moiety and lactobionic acid at the carboxyl group of vancomycin exhibited more than 1000-fold (MIC = 0.7 μM) and 250-fold (MIC = 1 μM) better activity against VanA and VanB strains of VRE, respectively, as compared with vancomycin. The incorporation of the lipophilic moiety into the glycopeptide-lactobionic acid scaffold imparted membrane interaction properties, resulting in improved activity against VRE (Yarlagadda et al. 2015a). Further, the pharmacokinetic and pharmacodynamic properties of this derivative were better than that of vancomycin (Yarlagadda et al. 2015b).