1.3.1 Exploitation of Carbohydrate Chemistry to Study Structure–Activity Relationship of Aminoglycoside Derivatives

As introduced in Section 1.1, aminoglycosides are small molecule drugs that contain carbohydrates as part of their core structure and possess several amino and hydroxyl functionalities (Figure 1.1). The chemical modification using carbohydrate chemistry has been applied to find the SAR and to design new molecules (Li and Tom Chang 2006; Guo et al. 2012; Matsushita et al. 2015; Thamban Chandrika and Garneau-Tsodikova 2018). The evidence from the mechanisms of molecular action and bacterial drug resistance showed that (i) the effectiveness of antibiotics is related to the amount of charge and the number of modifiable sites (e.g. AGAs with a higher number of amino groups can bind more strongly to RNA); (ii) ring I is the main target of inactivating bacterial enzymes, and ring III seems to be less sensitive to structural modifications; and (iii) the substitution of C-3′ or C-4′ hydroxyl groups can protect the antibiotics from APH and ANT enzymes, keeping the AGA activity.

Thus, the chemical strategies to address resistance mechanisms can include modification of the AGA core and insertion of substituents at different positions of AGA scaffolds, protecting the enzymatically modified sites and changing the hydrophobicity of the molecule; generation of new AGAs by glycodiversification and chemoenzymatic reactions; and synthesis of inhibitors for the modifying enzymes. The preparation of the AGA derivatives can be carried out using the AGA natural scaffold or by synthesis of AGA analogues. Here, we will highlight some examples; a more extensive review on these can be found in Guo et al. (2012) and Thamban Chandrika and Garneau-Tsodikova (2018). One example was the synthesis of kanamycin derivatives modified at C4′ position of ring I of the neamine moiety with different substituents to protect against the action of ANT(4′), APH(4′), or APH(3′) (Yan et al. 2011). Some of these derivatives exhibited antibiotic activity not only against nonresistant bacteria but also drug-resistant bacteria that express AMEs (e.g. those containing a nitrogen atom at the end and three carbon–carbon bonds between the end nitrogen atom and the carbonyl group). A second example was the synthesis of amide-linked aminoglycoside-CoA bi-substrates as inhibitors of AMEs (Gao et al. 2008). Most of these bi-substrates were competitive inhibitors of AAC(6′)-Ii in the nanomolar range. The crystal structure of the complexes revealed that they are good mimics of the enzymatic reaction intermediates. In a recent study, glycodiversification of paromomycin was carried out, leading to synthesis of a series of derivatives modified at the 4′-*O*-glycoside with different carbohydrates (Matsushita et al. 2015). The target selectivity to inhibit protein synthesis (i.e. inhibition of the bacterial ribosome over eukaryotic mitochondrial and cytosolic ribosomes with reduced toxicity) was greater for the equatorial than for the axial pyranosides and greater for the D-pentopyranosides than for the L-pentopyranosides and D-hexopyranosides. As an example,