resistance was largely overcome by introduction of AGAs derived from 2-deoxystreptamine (DOS) (Figure 1.1c), reviewed in (Davies 2007). These included neomycin (1949), kanamycin (1957), gentamycin (1963), tobramycin (1967), and sisomicin (1970). The acquisition of bacterial resistance for the DOS aminoglycosides prompted the development of novel and potent semisynthetic AGAs. These second-generation AGAs resulted from the insertion of a 4-hydroxy-2-aminobutyric acid (HABA) substituent of the C-1 amine group on the DOS ring of kanamycin and gentamycin-derived compounds. Examples are dibekacin (1971), amikacin (1972), arbekacin (1973), isepamicin (1975), and netilmicin (1976). However, because of their clinical usage, bacteria also developed resistance mechanisms against these semisynthetic antibiotics, almost leading to the abandon of AGAs.

Recently, the interest in AGAs research has resurged as consequence of the increasing number of strains resistant to other classes of antibiotics, such as the Gram-negative bacteria *Enterococcus faecium* responsible for serious invasive nosocomial infections (Buelow et al. 2017). New approaches have been used for developing semisynthetic AGAs using combined structure–activity relationship (SAR), in search for less toxic but effective AGAs (Thamban Chandrika and Garneau-Tsodikova 2018). The AGA plazomicin developed by Achaogen Inc. (ACHN-490) (Aggen et al. 2010), currently in phase III clinical trials, is an evidence of the renewed interest. Table 1.1 summarizes described AGAs and their distinctive features.

1.1.1 The Structure of Aminoglycosides

In this section, the basic structure of AGAs and the major differences between the various families and classes are overviewed. For a better understanding of the dissimilarities between them, a reference to the biosynthetic pathways is made. A more comprehensive review on the genetics and biosynthesis of AGAs is available in Piepersberg et al. (2007) and Becker and Cooper (2013).

As stated by their name, AGAs have in their composition amino-modified glycosides, which contain a carbohydrate linked to another functional group via a glycosidic bond. The common element to the core structure of the various AGA families is the *myo*-inositol (a cyclohexanehexol with six hydroxyl groups) (Figure 1.1a). AGA biosynthesis starts with a *myo*-inositol molecule and bifurcates into two distinct pathways that have (i) streptamine (Figure 1.1b) or (ii) 2-deoxystreptamine (2-DOS) (Figure 1.1c) as intermediates. Streptamine results from the introduction of an amino group at the 1,3-positions of the *myo*-inositol ring and is the intermediate of the streptamine-related AGA family. The few members of this family, including streptomycin, have the streptamine intermediate guanidinylated at the 3-position and a disaccharide unit linked to the 4-position (Figure 1.1d). For many AGA antibiotics, the core structure is the paromamine (Figure 1.1e), a pseudodisaccharide with the