2-DOS intermediate derivatized with glucose at the 4-position, ring II and ring I, respectively. Paromamine-related AGAs are the 4,5-disubstituted neomycin (Figure 1.1e) and the 4,6-disubstituted kanamycins and gentamycins. These AGA classes are also named after the following intermediate in the biosynthetic pathway – neamine, substituted at the 6′-position of ring I with an amine group (R1 substitution; Figure 1.1e).

The AGA classes with pseudodisaccharides other than paromamine comprise the family of fortimicin-related pseudodisaccharides, which include the fortimicin and istamycin. These are produced in a distinct biosynthetic pathway, although sharing some steps with the general 2-DOS and streptomycin biosynthesis. Another AGA family is the monosubstituted 2-DOS AGA family, which includes the hygromycins (Figure 1.1f) and the apramycins, containing the 2-DOS unit as central core with substitutions in the 5- and 4-positions, respectively. Few members of these two last families have clinical importance, except for spectinomycin.

1.1.2 Mechanisms of Action

The bacterial ribosome is the final target of the AGAs, more precisely the A-site located on the 16S RNA of the 30S bacterial ribosomal subunit, which is the binding site of a cognate transference RNA (tRNA) (Figure 1.2).

The elucidation of this macromolecular machine was accomplished by studying the mode of action of AGAs and other ribosome-targeting antibiotics. The bacterial ribosome is composed of 3 rRNAs and 54 ribosomal proteins. The rRNA molecules are the main players, interacting with the messenger RNA (mRNA) and tRNA molecules during protein synthesis. The study of AGAs also enabled to understand the efficiency and fidelity of the translation process, decoding mRNA into protein. The AGAs target the elongation cycle, resulting in a decrease of the fidelity of the ribosome (Figure 1.2a) or in complete inhibition of protein synthesis (Figure 1.2b). During the elongation cycle, the ribosome alternates between an unlocked and a locked structure. This interchange is important for mRNA and tRNA translocation and ribosome recycling. In the unlocked ribosome, the deacylated tRNA in the P-site allows incoming of the elongation factor G, promoting the conformational change. In the locked state, the peptidyl-tRNA in the P-site prevents movements between ribosomal subunits and therefore provides a stable architecture required for the rapid and accurate reading of the mRNA molecules (Valle et al. 2003).

AGAs interfere with the elongation cycle in different ways. For example, streptomycin binds to RNA helices h27, h18 (the 530 loop), and h44 and to the ribosomal protein S12, interfering with the delivery of the aa-tRNA to the A-site of the ribosome by the elongation factor Tu. The antibiotic stabilizes a conformation of the A-site that has higher affinity to tRNAs (including non-cognate tRNAs) and is thus more error-prone (Carter et al. 2000). The 2-DOS