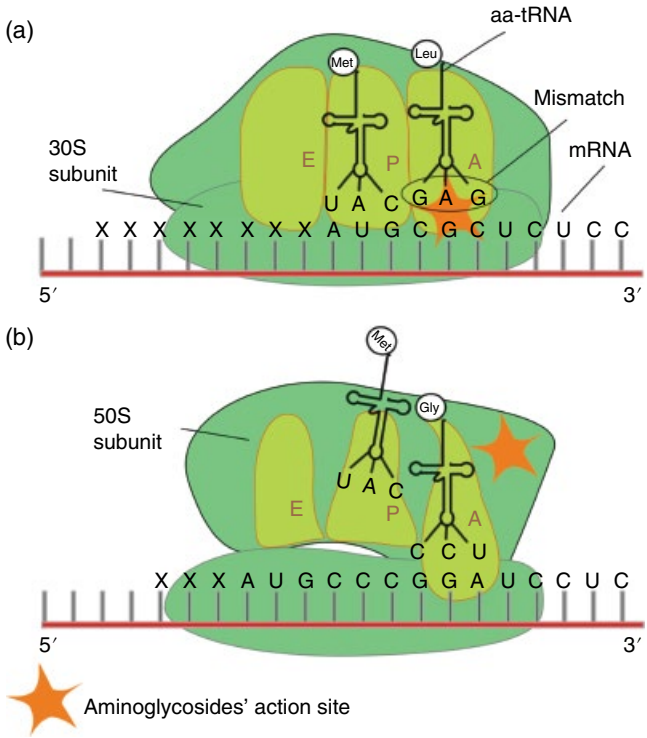

Figure 1.2 Schematic representation of the mode of action of AGAs in the bacterial ribosomes. During initiation, the small (30S) and large (50S) subunits bind, and the start codon of the mRNA is positioned along with the initiator aminoacylated tRNA (aa-tRNA) at the ribosomal P-site. In the elongation phase, an aa-tRNA is then delivered to the A-site, and the formation of a peptide bond between the amino acids attached to the tRNAs in the A- and P-sites occurs. The AGAs target the elongation cycle of protein synthesis by (a) increasing the error rate during the decoding process in the A-site and (b) inducing conformational changes in the 50S subunit, inhibiting the translocation of the tRNA molecules (from the A- and P-sites to the P- and E-sites).

AGAs such as hygromycin B, neomycin, and paromomycin inhibit the translocation of the tRNAs (catalyzed by the elongation factor G). These AGAs interact with the internal loop of h44 from the decoding center of the ribosome and stabilize a "flipped-out" conformation of the rRNA nucleotides A1492 and A1493. These local rearrangements of the highly conserved h44 impair the ribosome's ability to discriminate between cognate and non-cognate tRNAs, thus leading to an increase in the error rate (Carter et al. 2000; Borovinskaya et al. 2008; Wang et al. 2012). In addition to binding to h44 on the small subunit, neomycin has a second binding site within h69 of the 23S rRNA, which interacts with h44 of the 16S rRNA, creating an intersubunit bridge. In this