inactive up to 15 aminoglycosides from different classes. Although there are over 110 structures in Protein Data Bank related to aminoglycoside-resistance enzymes, there are fewer studies on the structure-based design of their inhibitors (Chiem et al. 2016; Garzan et al. 2016; Parulekar and Sonawane 2018). This suggests that there are opportunities to development of effective and potent inhibitors of aminoglycoside-modifying enzymes using integrated approaches discussed earlier.

13.6 Antimicrobial Peptides

AMPs are generally short peptides with sequences that are less than 50 amino acids in length. Those molecules are often found in living organisms and part of a defense mechanism against bacterial infections (Ageitos et al. 2017). AMPs are being considered as an alternative to antibiotics or as a component of combination therapy with classic antibiotic (Figure 13.1h). These molecules are generally cationic and can adopt linear or cyclic structures. A judicious analysis of short AMPs (comprising <15 amino acids) with proven activity against Gram-negative bacteria has shown that these molecules form amphipathic surfaces via formation of either alpha helical or beta-turn structure (Passarini et al. 2018). However, there is a limited application of pure AMPs in the clinic due to their poor pharmacokinetic profiles or toxicity despite their observed promising activities against a range of different bacteria, but they can provide the basis for the design of novel modified peptides or peptidomimetic compounds. However, as the mechanism of action of AMP is commonly directed toward disruption of the membrane via various mechanisms or unknown (Ageitos et al. 2017; Kumar et al. 2018), the conventional structure-based design of peptides is not adequate, but other approaches are being employed.

Conformational studies of AMPs in the absence and presence of micelles are often conducted by NMR spectroscopy that provides not only structural information in a similar way as X-ray crystallography but can also provide information about their flexibility in different environments, particularly in the case of linear peptides (Vermeer et al. 2012). These conformational changes can be explored by using molecular dynamics simulations, which may provide information on their mechanism of action (Marquette and Bechinger 2018; Montales et al. 2018; Strandberg et al. 2018) and interactions with the membrane (Berglund et al. 2015; Balatti et al. 2017; Ulmschneider and Ulmschneider 2018). However, there is a need for continuous improvement and validation of methods and force fields used for conducting these types of simulations to ensure the reliable representation of the experimental observations (Wang et al. 2014). Although there are some successes in their modifications guided by molecular dynamics AMPs to change their activity (Waghu et al. 2018) or to reduce side effects (Dubovskii et al. 2018), the duration of molecular dynamics