(Schillaci et al. 2017). The main reason behind antibiotic resistance are (Walsh 2000; Soon et al. 2011; Blair et al. 2015; González-Bello 2017):

- Removal of the antibiotic from the bacteria by membrane transporters named efflux pumps (Figure 13.1a).
- Decrease of drug uptake by modification of porin transporters and/or by modification of the surface charge of the Gram-negative bacteria and consequently reducing colistin binding (Figure 13.1b).
- Expression of enzymes that change or degrade antibiotics rendering them inactive (Figure 13.1c).
- Change of the structure binding site of the target biomolecule, so that antibiotics cannot exert its activity (Figure 13.1d).

While the pharmaceutical approaches and other alternative technologies to target antibiotic resistance were discussed elsewhere (Schillaci et al. 2017; Baker et al. 2018), the focus of this chapter is on the computer-aided drug design (CADD) of small molecules to overcome bacterial resistance. These approaches and methods are used with intention to develop new antibiotics by utilizing new targets, to discover new inhibitors of efflux pumps and drug-modifying enzymes, and to design novel antimicrobial peptides (AMPs).

13.2 Drug Design Principles

The drug design is a process of finding a molecule, known as a ligand or hit molecule, which has a potential to inhibit or enhance the activity of a targeted biomolecule through specific interaction and often tight binding (Figure 13.1c–e). This requires complementarity in shape and charges at the ligand–biomolecule interface. A hit molecule is subjected to limited optimization to develop a lead molecule with improved physicochemical properties and bioavailability. A lead molecule, promising drug candidate, can be considered for further process of drug development through optimization of its activity and metabolic half-life while minimizing side effects through iterative medicinal chemistry efforts during preclinical trials.

The plethora of the information available on molecular properties of potential drug candidates, their activities against different bacterial strains, mechanisms of action, target structures, and biochemical pathways can be optimally utilized to specifically interfere with bacterial cellular processes (Zloh and Kirton 2018). Molecules can be designed to interfere with the function of a biomolecular target that is associated with the survival of a microbial pathogen while designing out undesirable off-target interactions with the host. Approaches that can be utilized depend on the available information related to the selected target and pathogen of interest (Figure 13.2). Some general information and overview of methods used in CADD can be found elsewhere (Zhang 2016; Yu and MacKerell 2017).