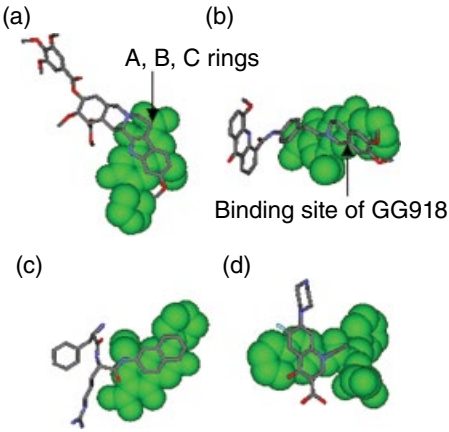

Figure 13.7 Highest interaction energy complexes between MDR inhibitors and substrates for bacterial MDR (substrate molecules are represented as spheres). (a) reserpine strongly binds norfloxacin at the same binding site for anticancer drugs, namely, rings A, B, and C. (b) Binding site of GG918 for norfloxacin is the same as for the topotecan complex. (c) The aromatic moiety of the MC-207,110 strongly binds the antibiotic levofloxacin. (d) The interaction between MC-002,595 and NPN involves π–π stacking of the aromatic rings. Source: Reprinted with permission from Zloh et al. (2004). Copyright (2004) Elsevier.

13.5 Design of Inhibitors of Drug-Modifying Enzymes

Bacterial resistance mechanism that is most clinically relevant is caused by the enzymatic modifications of antibiotics. To protect itself, bacteria can acquire and produce an enzyme that changes the chemical structure of an antibiotic and prevents its interaction with the target. Such an enzyme can degrade an antibiotic by hydrolysis (for example, β-lactamases) or add a chemical group(s) (for example, aminoglycoside-modifying enzymes) (Blair et al. 2015).

Such enzymes have distinct active sites that bind antibiotics, which may potentially be targeted by new molecular entities acting as inhibitors of such enzymes. These molecules would be suitable for developing combination therapies, where co-administration of an inhibitor with an antibiotic would restore its activity. These inhibitors generally mimic the shape and charges of antibiotic, which preferably bind into the enzyme binding site over antibiotic. A knowledge of the enzyme structure and its interactions with the antibiotics would, therefore, facilitate the design of effective adjuvants for combination therapies.

One of the mechanisms of resistance against β-lactam antibiotics is their degradation by one or more β-lactamases for which combination therapies are already developed and commercially exploited (Buynak 2006). Despite the