M_1, pristinamycin II_A, pristinamycin II_B, and pristinamycin II_B derivative (dalfopristin), and group B streptogramins (cyclic hexadepsipeptides) with virginiamycin S and pristinamycins I_A, I_B, and I_C as the principal compounds. In addition, quinupristin is a pristinamycin I_A derivative. Both macrocyclic components inhibit bacterial protein synthesis at the level of the ribosome and have bacteriostatic activity and bactericidal activity when combined.

19.4.2 Pairing of Antibiotic with Nonantibiotic

The pairing of antibiotic with non-antibiotic adjuvants can restore or enhance the activity of older antibiotic, or also extend the spectrum of activity. Nonantibiotic adjuvants can function either by (i) affecting a vital physiological bacterial function; (ii) inhibition of antibiotic resistance elements; (iii) enhancement of the uptake of the antibiotic through the bacterial membrane; (iv) inhibition of efflux pumps; and (v) changing the physiology of resistant cells (dispersal of biofilms).

19.4.2.1 Affecting a Vital Physiological Bacterial Function

Molecules that alter bacterial cell shape by blocking cytoskeleton proteins and/or peptidoglycan biosynthesis and that act synergistically with the antibiotic have been also identified. Compounds 1, A22, pivmecillinam, and echinomycin are shown to be synergistic with novobiocin, including inhibitors of the bacterial cytoskeleton protein MreB and/or cell wall biosynthesis enzymes, in *Escherichia coli*.

19.4.2.2 Inhibition of Antibiotic Resistance Elements

One of the most successful and clinically used strategies has been the combination of a β-lactam antibiotic (inhibit to cell wall biosynthesis) with a β-lactamase inhibitor adjuvant (clavulanic acid, tazobactam, and sulbactam), of which the classical example is Augmentin. The β-lactamase inhibitor enhances the action of the β-lactam antibiotic by inhibiting the β-lactamase activity, thus restoring the antibiotic activity against β-lactamase-producing pathogens. Augmentin was the best-selling antibiotic in 2001, demonstrating the effectiveness of the approach of combining an antibiotic and adjuvant in clinical settings.

Previous reports have shown that the novel bicyclic penem β-lactamase inhibitors (BLI-489) conferred activity and efficacy as an inhibitor of class A including extended-spectrum β-lactamases (ESBLs), class D, and class C β-lactamase enzymes, while the tricyclic carbapenem inhibitor LK-157 has also shown promising activity against various ESBLs.

NXL104 (avibactam) is a broad-spectrum non-β-lactam β-lactamase inhibitor that has been shown to restore cephalosporin susceptibility to a large number of ESBL-producing *E. coli* and *Klebsiella pneumoniae* strains. Avibactam in