also able to show that neutropenic mice infected with *E. coli* showed synergistic effects between OAKs and erythromycin, without any visible toxicity (Goldberg et al. 2013).

The majority of work has been placed on the third group of inhibitors, those that directly inhibit pump function (Lomovskaya and Bostian 2006; Mahamoud et al. 2007, 2016; Pages et al. 2008; Pages and Amaral 2009). A large number of efflux pump inhibitors (EPIs) that directly affect pump function have been produced and are divided in four major classes. In the first group, peptidomimetics produced from the study of efflux pump function have shown synergistic effects with a variety of antibiotics against Gram-negative bacteria (Lomovskaya and Bostian 2006; Mahamoud et al. 2007 and references therein). The best characterized molecule is phenylalanine arginine beta-naphtylamide (PAβN) that sensitizes *P. aeruginosa* to levofloxacin (Lomovskaya et al. 2001) as well as other Gram-negative organisms against several classes of antibiotics (Lomovskaya and Bostian 2006). This approach suffers from problems with high toxicity, making it impossible for these compounds to be used in the clinic thus far.

A second class of compounds that have been gaining attention is quinoline derivatives that show broad-spectrum sensitization of *Enterobacter* spp. and *K. pneumoniae* to various antibiotics (Chevalier et al. 2004). These compounds have less activity against some classes of transporters, especially those expressed by *P. aeruginosa* (Mahamoud et al. 2007), and their toxicity to human cells is a major hurdle in their development.

The third class of inhibitor containing acylpiperidines and arylpiperazines and their derivatives have showed promising effects on efflux pump inhibition in both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*E. coli*) bacteria, for example, reversing antibiotic resistance of *E. coli* to linezolid (Thorarensen et al. 2001). It is unclear how they work, however, as treatment with these EPIs did not produce significant increase in intracellular antibiotic concentration, which would be expected of an EPI. Although they work effectively on *Enterobacteriaceae* and *A. baumanii* (two of the critical priority pathogens on the WHO list (Tacconelli et al. 2017)), they had poor activity against the third critical pathogen *P. aeruginosa*.

Finally, other compounds have also been discovered. Dwivedi et al., showed that urosolic acid derivatives can inhibit efflux pump activity both through inducing a reduced expression of efflux pump genes and by inhibition of the efflux pump ATPase itself (Dwivedi et al. 2014). This approach sensitized *E. coli* to nalidixin and tetracycline *in vitro*. Another study shows that a group of compounds already used for other indications (chlorpromazine, amitryptiline, and transchlorprothixene) also have EPI activity and can sensitize several bacteria to antibiotics (Kristiansen et al. 2010). These substances have already been used clinically for years, proving their safety, but their alternative use may not be without obstacles due to higher concentrations needed for sensitization