

## Chapter 35

# QSAR Studies on Bacterial Efflux Pump Inhibitors

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### ABSTRACT

*Antimicrobial drug resistance occurs when bacteria undergo certain modifications to eliminate the effectiveness of drugs, chemicals, or other agents designed to cure infections. To date, the burden of resistance has remained one of the major clinical concerns as it renders prolonged and complicated treatments, thereby increasing the medical costs with lengthier hospital stays. Of complex causes for bacterial resistance, there has been increasing evidence that proved the significant role of efflux pumps in antibiotic resistance. Coadministration of Efflux Pump Inhibitors (EPis) with antibiotics has been considered one of the promising ways not only to improve the efficacy but also to extend the clinical utility of existing antibiotics. This chapter begins with outlining current knowledge about bacterial efflux pumps and drug designs applied in identification of their modulating compounds. Following, the chapter addresses and provides a discussion on Quantitative Structure-Activity Relationship (QSAR) analyses in search of novel and potent efflux pump inhibitors.*

### INTRODUCTION

Antimicrobial drugs have been important tools of healthcare in several decades because of their effectiveness in control of bacterial infections. Unfortunately, soon after their invention it was realized that some pathogens rapidly developed resistance to antibiotics (Neu, 1992; Wood, Gold, & Moellering Jr, 1996). People infected with antimicrobial-resistant organisms are more likely to have longer, more expensive

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hospital stays, and may be more likely to die as a result of the infection. Initially, this problem was overcome by discovery of new classes of antibiotics such as aminoglycosides, macrolides and glycopeptides, but the bacteria rapidly showed an impressive array of defensive mechanisms that conferred on them, resistance to many modes of attack (Wood et al., 1996). The main mechanisms whereby the bacteria develop resistance to antimicrobial agents include enzymatic inactivation (Bush & Miller, 1998; Sabatini et al., 2012), modification of the antibiotic attack site(s) (Ruiz, 2003; Sabatini et al., 2012), and reduction of intracellular drug concentration by changes in membrane permeability (Nikaido, 2003; Sabatini et al., 2012) or by the overexpression of efflux pumps (Li & Nikaido, 2009; Sabatini et al., 2012).

One primary mechanism of antibiotic resistance is extrusion of the foreign chemical, which is termed efflux. In 1980, tetracycline was reported that it could be actively effluxed from the bacterial cell (McMurry, Petrucci, & Levy, 1980). From then on, many efflux-related mechanisms have been discovered. Overexpression of these efflux pumps may lead to antibiotic resistance. While efflux pump proteins are present in both Gram-positive and Gram-negative bacteria and also in eukaryotes, antibiotic resistance due to efflux is more of a problem in Gram-negative bacteria than in Gram-positive bacteria (Nikaido, 1996). This is because the presence of an outer membrane in Gram-negative bacteria shows comparatively lower permeability and complements the efflux activity of these pumps. Besides, studies of efflux pumps in Gram-negative bacteria have got more complicated as their double-membrane cells allow the expression of a tripartite efflux pump system such as AcrA/AcrB/TolC in Enterobacteriaceae, or MexA/MexB/OprM in *Pseudomonas aeruginosa*. One plausible practice to fight against multidrug efflux systems (MES) is the combination of conventional antimicrobial agents/antibiotics with small molecules that block MES known as multidrug efflux pump inhibitors (EPIs). An array of approaches in academic and industrial research settings, varying from high-throughput screening (HTS) ventures to bioassay guided purification and determination, have yielded a number of promising EPIs in a series of pathogenic systems (Tegos et al., 2011).

Up to now, most inhibitors of efflux pumps have been discovered through traditional random screening of synthetic compounds or natural products libraries. The assays used are very simple and easily adapted to high-throughput screening. An alternative approach is to screen libraries of known drugs. The identification of a novel mode of action in an approved drug could considerably shorten the development route and lessen the risks associated with a new chemical entity.

## **OVERVIEW OF BACTERIAL EFFLUX PUMPS AND ANTIBIOTIC RESISTANCE**

### **Bacterial Efflux Pumps**

Efflux pumps in Gram-positive bacteria can be categorized into four families (Handzlik, Matys, & Kieć-Kononowicz, 2013), namely ABC (ATP-binding cassette) (Higgins, 2001), MFS (major facilitator superfamily) (Saier Jr et al., 1999), SMR (small multidrug resistance) (Chung & Saier Jr, 2001) (Jack, Yang, & H Saier, 2001), and MATE (multidrug and toxic compound extrusion) (Hvorup et al., 2003).

For Gram-negative bacteria, many pump systems including *Campylobacter jejuni* (CmeABC) (Pumbwe & Piddock, 2002) (Lin, Michel, & Zhang, 2002), *Escherichia coli* (AcrAB-TolC, AcrEF-TolC, EmrB, EmrD) (Poole, 2000), *Pseudomonas aeruginosa* (MexAB-OprM, MexCD-OprJ, MexEF-OprN and MexXY-OprM) (Poole, 2000), *Salmonella typhimurium* (AcrAB) (Nikaido, 2001) have been described. These pumps basically belong to five major families, including the MFS (major facilitator superfamily),

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