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AR Mechanism-Based Drug Design

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13.1 Introduction

Antibiotic agents currently used in the clinic disrupt biosynthesis of essential cell components (metabolites, proteins, peptidoglycans, and DNA) in actively growing bacteria and can also affect DNA replication and cell wall formation (Chopra et al. 2002; Kohanski et al. 2010). Although most of these drugs generally stimulate hydroxyl radical formation and induce a common oxidative damage cellular death pathway (Kohanski et al. 2007, 2008), they form interactions with different cellular targets. The discovery of antibiotic agents initially relied on serendipity and empirical screening of natural products for their ability to inhibit bacterial growth during "golden era" of antibiotic discovery. This period was followed by a period of rational drug design where new therapeutic agents were developed by modification of existing antibiotics mainly without knowledge of their site of action (Aminov 2010). Computer-aided molecular design approaches in combination with genomics-based identification of targets were further employed from the early 1990s, however with the limited success in the discovery of novel classes of antibiotics (Simmons et al. 2010; Brown and Wright 2016). The agents that entered the full development since 1995 were mostly from the already known classes of antibiotics (Bush 2012).

Bacteria's ability to respond to stresses and challenges by toxic compounds, which include antibiotics, results in resistance to therapies. Defense mechanisms can be developed from the presence of intrinsic genes in their genome that could generate a resistance phenotype and from the mutations in chromosomal genes (Davies and Davies 2010), as well as due to horizontal gene transfer (HGT) responsible for increased propagation of

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