Structure of macrolide dirithromycin as a basis for the design of novel potent translation inhibitors

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The emergence of microbes that are able to resist most of the antibiotics used in clinical practice (so-called multidrug-resistant organisms, or MDROs) is a crucial challenge for medical society and researchers in related fields. Whilst the most common way to slow down the growth of MRDOs is through proper hygienic and optimal therapeutic regimen, a search for a new antimicrobial agent that would be able to defeat current resistance could be a key solution to this significant problem.

A prominent branch of antimicrobial drug design is the development of novel macrolides antibiotics. A core of their structure is a large (14-, 15- or 16-membered) lactone ring carrying various functional groups. Most of the macrolides act either by disrupting binding of peptidyl-tRNA to the bacterial ribosome or by interfering with the passing of nascent protein chain through the ribosomal tunnel. Because of such high-conservative target, this mechanism implies small chance of emergence of resistance to the drug. Nevertheless, there are several ways for resistance to occur, leading to serious problems in clinical practice.

In this work, we propose the structure of dirithromycin (dir), an analog of widely used macrolide erythromycin, as a starting point for the further design of translation inhibitors. Data obtained in vitro and in vivo show that dir binds to the ribosome stronger than erythromycin. It is confirmed by the x-ray structure of the dir-ribosome complex. Therefore, further modifications of dir molecule could significantly enhance its potency and lead to the new generation of effective antimicrobials, making a breakthrough in our fight with resistance.