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Abstract

Chloramphenicol and Metronidazole Derivatives of Azithromycin Overcome the Inducible Resistance to Macrolide Antibiotics †

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Abstract: The emergence and rapid development of microbial resistance to antibacterial drugs is one of the major problems for modern science and medicine. One of the methods being developed to address the problem is the design of hybrid antibacterial substances based on two different pharmacophores covalently linked to each other. In this work, we synthesized and characterized two sets of hybrid compounds, in which azithromycin at the 4″-position was bound to chloramphenicol or metronidazole using linker fragments of different length and structure. Almost all conjugates were shown to efficiently inhibit protein synthesis in vitro in a cell-free bacterial translation system similar to azithromycin. Moreover, we demonstrate that novel derivatives of azithromycin are active against *Escherichia coli* strain inducibly resistant to macrolide antibiotics due to the *ermCL*-dependent regulation of ErmC methyltransferase synthesis. Further toe-printing analysis revealed a premature ribosome stalling at the Phe codon (UUU), as well as the absence of ribosome arrest at positions characteristic of azithromycin (and crucial for the regulation or ErmC synthesis) in the presence of hybrid compounds. Thus, we demonstrate that novel derivatives of azithromycin have a preference to cause premature ribosome stalling during translation, which makes them active against bacterial strains inducibly resistant to the typical macrolide antibiotics.

Keywords: hybrid antibiotics; azithromycin derivatives; macrolide antibiotics; mode of action; drug resistance

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