Synthetic analogues of ribosomal antibiotics

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The ribosome is an important molecular machine that synthesizes proteins. Peptide synthesis occurs in peptidyl transferase center (PTC), and the ribosome nascent peptide exit tunnel (NPET) controls peptide synthesis and provide exit of nascent peptide from the ribosome. Binding sites of many antibiotics are located in the NPET. That is why modification of some rRNA bases can lead to antibiotic resistance. Sometimes strong interaction between rRNA bases of NPET and nascent peptide chain leads to translation stalling. Synthetic analogues (SA) of ribosomal antibiotics can be used to study the interaction of antibiotics and peptides with NPET. SA constructed for this purpose consist of a peptide and an antibiotic parts, the first simulates nascent peptide chain, and the second serves as an "anchor" that binds with the ribosome. The study of the binding between such compounds and NPET may shed light on the features of the interaction of NPET walls elements with specific groups of the peptide and the antibiotic. In addition, such SA provide a platform for the creation of new antibiotics that could act against resistant strains of bacteria.

The objects of our study are peptide derivatives of desmycosin (Des)–macrolide antibiotic, and chloramphenicol (CLM), containing oncocin (Onc) residues in their structures. Onc is antimicrobial peptide, mechanism of its action is associated with translation stalling. It has been found that Onc binds in the ribosome extending from the PTC to the exit from NPET thusoverlapping binding sites of a number of ribosome antibiotics including macrolides and CLM. In view of these facts, on the basis of computer modeling based on the crystallographic data obtained for complexes of bacterial ribosomes with antibiotics or Onc, we constructed SA, in which structures peptide fragments of Onc are linked with 4'-hydroxyl group of Desor amino group of chloramphenicol amine (CAM) through suitable linker. Des derivatives contain N-terminal Onc fragments, CLM derivatives comprise Onc fragments, located closer to C-terminus. A series of 4'-desmycosin derivatives, containing 1-6, 2-6, 3-6, 4-6 and 5-6 fragments of Onc, and CLM analogues, comprising 8-10 peptide fragments are synthesized. The peptide fragments of Onc and CAM-oncocin derivatives were synthesized by solid phase synthesis on 2-ClTrt resin using Fmoc/Boc(Pbf/tBu) strategy. Des-oncocin derivatives were obtained by conjugation of protected peptides with Des, modified by GABA at 4'-OH. The binding ability of SA of ribosomal antibiotics was studied by displacement of the fluorescent erythromycin analog from its complex with *E. coli* ribosomes. To assess the abilities of these analogues to inhibit protein synthesis we used double-reporter system pDualrep2.