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New approach in discovering tylosin like antibiotics

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Nascent protein chains could modulate their own translation by interacting with ribosomal exit tunnel. It was found that critical residue for such self-modulating peptides is tryptophan[1]. New generation antibiotics could be constructed with this feature utilization. Fusion molecules on base of such self-modulating peptide and macrolide containing antibiotics could be designed, where new molecule targets ribosome exit tunnel twice, first with macrolide part and second with peptide part.

The main goal of this work is to simulate such fusion-molecules and determine contacts are critical for binding and suggest new antibiotic like molecules based on simulations analysis.

Tylosin was selected as starting molecule. 3D structure of ribosome with tylosin was solved before [2]. Simulations system consisted of ribosome residues which were found around of tylosin and various tylosine derivatives in radius of 20 angstrem . Used derivatives consisted of macrolide and substitution groups acting as self-modulating peptide. New approach of using distance constraints was developed for ribosome in order to simulate rest of ribosome. All computional experiments were done using molecular dynamic simulation programs suite Gromacs [3,4,5,6]. Five systems was subjected for molecular dynamics simulation with trajectory length 200 ns on "Chebyshev" supercomputer.

The analysis of trajectory revealed critical contacts between ribosome and fusion molecules. Tylosin like part of a molecule serves as anchor that forms non-covalent interactions with ribosomal tunnel and holds molecule in a right orientation. For peptide part of molecule was found that presence of tryptophan residue is critical, because it forms stacking interactions with cation-pi interaction to L22 subunit of ribosome and that could play a role stalling translation of nascent chain.

The goal of this work was reached and for complex of ribosome and molecules of interest critical contacts for good binding were found. Furthermore, the base for successful design of new antibiotic compounds was established. This methodology could be easily extrapolated to other known huge macromolecules in order to develop future inhibitors and probably drugs.

Литература

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