

## Developing Novel Bacterial Primase (DnaG) Inhibitors

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**Abstract :** The plummeting number of infections and death is due to the development of drug-resistant bacteria. In addition, the number of approved antibiotic drugs by the Food and Drug Administration (FDA) is insufficient. Therefore, developing new drugs and finding novel targets for central metabolic pathways in bacteria is urgently needed. One of the promising targets is DNA replication machinery which consists of many essential proteins and enzymes. DnaG primase is an essential enzyme and a central part of the DNA replication machinery. DnaG primase synthesizes short RNA primers that initiate the Okazaki fragments by the lagging strand DNA polymerase. Therefore, it is reasonable to assume that inhibition of primase activity will stall DNA replication and prevent bacterial proliferation. We did the expression and purification of eight different bacterial DnaGs (Mycobacterium tuberculosis(Mtb), Bacillus anthracis (Ba), Mycobacterium smegmatis (Msmeg), Francisella tularencis (Ft), Vibrio cholerae (Vc) and Yersinia pestis (Yp), Staphylococcus aureus(Saureus), Escherichia coli(Ecoli)) followed by the radioactive activity assay. After obtaining the pure and active protein DnaG, we synthesized the inhibitors for them. The inhibitors were divided into five different groups, each containing five molecules, and the cocktail inhibition assay was performed against each DnaGs. The groups of molecules inhibiting the DnaGs were further tested with individual molecules belonging to inhibiting groups. Each molecule showing inhibition was titrated against the corresponding DnaGs to find IC50. We got a molecule(VS167) that acted as broad inhibitors, inhibiting all eight DnaGs. Molecules VS180 and VS186 inhibited seven DnaGs (except Saureus). Similarly, two molecules(VS 173, VS176) inhibited five DnaGs (Mtb, Ba, Ft, Yp, Ecoli). VS261 inhibited four DnaGs (Mtb, Ba, Ft, Vc). MS50 inhibited Ba and Vc DnaGs. And some of the inhibitors inhibited only one DnaGs. Thus we found the broad and specific inhibitors for different bacterial DnaGs, and their Structure-activity analysis(SAR) was done. Further, We tried to explain the similarities among the enzyme DnaGs from different bacteria based on their inhibition pattern.

**Keywords :** DNA replication, DnaG, okazaki fragments, antibiotic drugs

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