STRUCTURAL AND FUNCTIONAL STUDIES ON 4-HYDROXY-TETRAHYDRODIPICOLINATE REDUCTASE: POTENTIAL DRUG TARGET IN BACTERIA

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Abstract

Antimicrobial resistance has become an alarming public health concern in recent times. Infections caused by multidrug resistant bacteria not only increase the mortality rate but also increase the economic burden globally. One approach to alleviate this issue is to find novel drug targets. In this regard, the bacterial lysine biosynthesis pathway provides several targets that may be used for design of antimicrobial compounds. Bacteria use lysine or meso-diaminopimelate to crosslink the peptidoglycan monomers in the bacterial cell wall. As such, we hypothesize that blocking this pathway will induce defects in the bacterial cell wall that are similar to those caused by β-lactam antibiotics. This study is directed towards identifying the potential of 4-hydroxy-tetrahydrodipicolinate reductase (DapB), an enzyme from lysine biosynthesis pathway as a drug target. DapB is a tetrameric enzyme that catalyzes NAD(P)H dependent reduction of (2S, 4S)-4-hydroxy-2,3,4,5-tetrahydrodipicolinate to generate 2,3,4,5-tetrahydrodipicolinate. This research uses biophysical and biochemical techniques to study the structures of these enzymes and identify potential inhibitory compounds. Interactions of DapB with cofactors and potential inhibitors are described. Major emphasis is on studies of DapB from Neisseria gonorrhoeae. Additionally, DapB enzymes from Mycobacterium tuberculosis and Vibrio vulnificus are also discussed.