STRUCTURE-BASED DRUG DESIGN OF NEW DXR-INHIBITORS AS ANTI-INFECTIVE AGENTS

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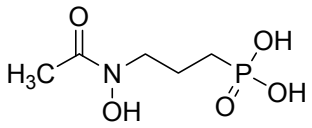
In spite of half a century development of antibiotics infectious diseases still pose one of the most serious health problems due to the unavoidable development of resistant germs. Therefore, increased efforts in anti-infective drug discovery are urgently needed. Enzymes involved in the nonmevalonate (DOXP/MEP) pathway of isoprenoid biosynthesis pathway are promising targets for the development of anti-infective agents [1], since this pathway is present in many pathogenic micro-organism while absent in humans.

Fosmidomycin and FR900098 are well-known as potent inhibitors of 1-desoxy-D-xylulose-5-phosphonate (DOXP) reductoisomerase (DXR), one enzyme of the DOXP/MEP pathway. However, their effectiveness against certain pathogens is hampered by their high polarity.

Based on crystal structures and flexible docking, we designed FR900098 derivatives with reduced polarity.



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[1] Jomaa, H. *et al.*, *Science*, **1999**, *285*, 1573-1576.