

Youngstown State University Chemistry
Seminar Program - Fall 2005

Friday November 4th (3:15)



7th Fall Seminar

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***“Mining New Microbial Pathways:
Identification and Target Validation”***

Abstract

The results from studies investigating the structure-function, enzyme mechanism as well as synthesis of potential inhibitors of the enzymes, 3-deoxy-D-arabino-heptulosonate-7-phosphate synthase (DAHPS), the first enzyme in the shikimate pathway, and 3-deoxy-D-manno-octulosonate-8-phosphate synthase (KDOPS), the second enzyme in the lipopolysaccharide biosynthetic pathway of Gram (-) bacteria, will be presented. Both these enzymes are potential targets for the design of a new generation of antimicrobial agents, biorationally designed, since both pathways are absent in mammals. The first example is drawn from the common biosynthetic pathways of glucose, aromatic amino acids, cofactors, etc., namely the Shikimic acid biosynthetic pathway. For this highly species specific pathway (e.g., the source of Roundup'sTM effectiveness), the role of DAHPS - its first enzyme, and how this specificity can be exploited in the search for medicinal chemistry targets will be discussed. The second pathway to be discussed is the synthesis of lipopolysaccharides in Gram negative bacteria. The structurally related enzyme, KDOPS, plays a key role in this bacterial pathway and is a similarly rich source of medicinal chemistry targets.

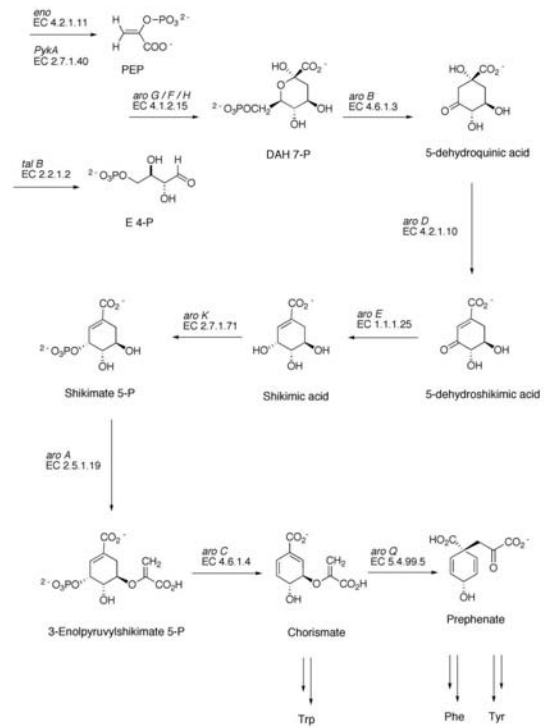


Figure 1. Shikimate Biosynthetic Pathway.

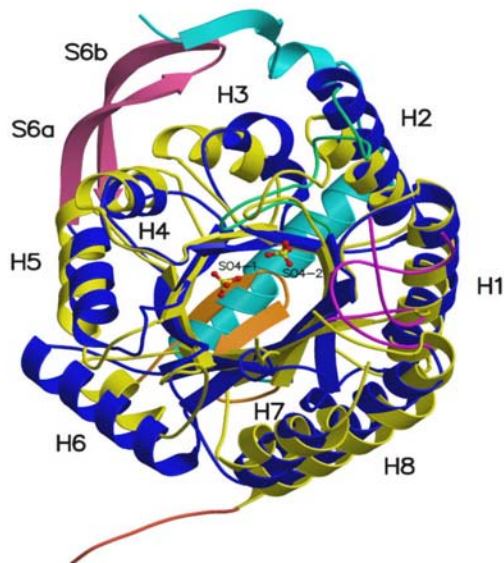


Figure 3. The Overlay of the Crystal Structures of DAHPS (blue) and KDOPS (maize).

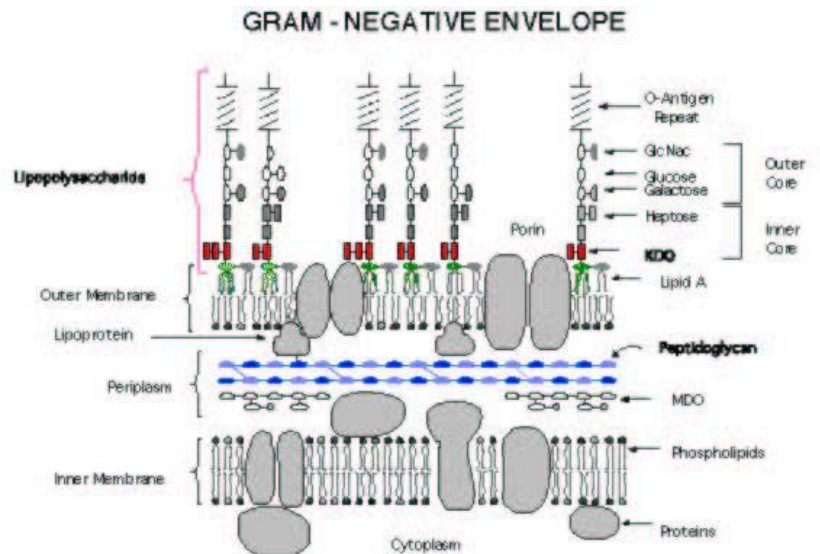


Figure 2. Gram Negative Envelope – *E. coli*