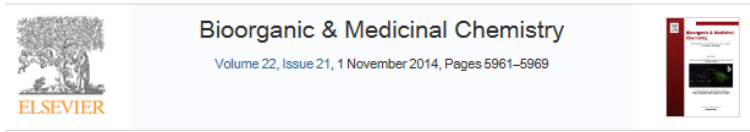
# Transient Kinetics of Siderophore Biosynthetic Enzymes

## *Background*

- Antibiotic resistance is a growing health concern, and new avenues of antimicrobial drug design are being actively sought.
- One suggested pathway to be targeted for inhibitor design is that of iron scavenging through siderophores.
- Bacterial pathogens require iron to colonize the human host.
- Prevention of nutrient acquisition has long been considered a viable method for identifying novel methods of antibiotic/ antimicrobial drug design.
- The goal of this work was to find lead compounds for the inhibition of the iron acquisition system mediated by small molecule iron chelators called siderophores.




**Expanding the results of a high throughput screen against an isochorismate-pyruvate lyase to enzymes of a similar scaffold or mechanism**

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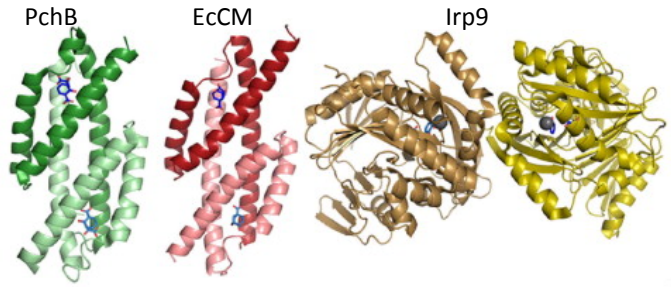


Enzyme scaffolds and transition states. The X-ray crystallographic structures for PchB (PDB code: 3REM) with salicylate and pyruvate bound, EcCM (1ECM) with Bartlett's TSA inhibitor bound, and Irp9 (2FN1) with $Mg^{2+}$, salicylate and pyruvate are depicted as cartoons. Each of these enzymes is a homodimer, with one monomer shaded darker than the other, and the active sites identified by the ligands shown as sticks. PchB and EcCM share the same fold—they are AroQ enzymes, whereas Irp9 is in the MST family of enzymes. The transition states for the reactions catalyzed, isochorismate-pyruvate lyase (left) and chorismate mutase (right), are shown below. The transition states are similar, differing only in the alignment of the pyruvylenol tail over the ring to make a cycle at the 1 (mutase) or 2 (lyase) carbon. PchB and Irp9 perform the same chemistry using different scaffolds, whereas PchB and EcCM perform related reactions in the same scaffold. It should be noted that PchB has adventitious mutase activity, albeit very low.

## *Advance*

- New antimicrobial lead compounds have been identified for the bacterial pathogens *P. aeruginosa, E. coli,* and *Y. enterocolitica* based on the inhibiting the siderophore biosynthetic pathways.
- A hig hthroughput screen against one enzyme was used to identify compounds that could serve as inhibitors against enzymes of similar fold or performing related chemistry.
- Lead compounds that inhibit the isochorismate-pyruvate lyase from *P. aerginosa,* the salicylate synthase from *Y. enterocolitica,* and the chorismate mutase from *E. coli* also promote growth inhibition in these pathogens.

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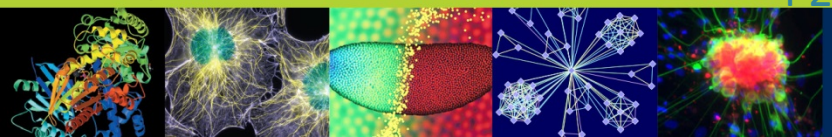

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