E. coli vs. P. aeruginosa deacetylase LpxC inhibitors selectivity: Surface and Cavity depth based analysis

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Introduction

- The deacetylase LpxC enzyme is present in *E. coli* and has been demonstrated to be essential for it's growth. It catalyses the first committed step of lipid A biosynthesis in the cell wall, which serves as a permeability barrier that protects the bacterium from many antibiotics, such as erythromycin.[1]
- LpxC has been identified in a gram-negative pathogen *Pseudomonas aeruginosa* which has been documented as a therapeutic problem because of nosocomial infection and antimicrobial resistance.
- The LpxC protein of *P. aeruginosa* is encoded by a homologous gene and catalyzes the same reaction as in *E. coli*. These data on sequence similarity and functional identity suggest that it should be possible to discover LpxC inhibitors active against both *E. coli* and *P. aeruginosa*. However, none of the early *E. coli* LpxC inhibitors, were able to inhibit the growth of *P. aeruginosa*.[3]
- Aim of this work was to study the potentially important structural differences in active sites of both proteins responsible for making the inhibitors selective for *E. coli* as compared to *P. aeruginosa* LpxC.

Methodology

- **Homology modeling:** Homology models for the LpxCs of both organisms were developed and validated on the basis of a 3D profile and PROCHECK.
- **Molecular electrostatic potential (MEP) based surface and cavity-depth analysis**
- **Docking:** A cross-docking analysis of reported inhibitors for both proteins was performed to reveal selective binding modes.

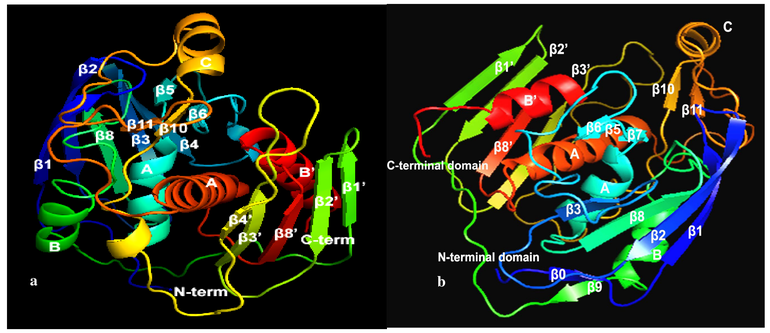
Homology modeling

- Template Selection

Name	Source	Local Identity (%)	PDB ID	Resolution (Å)
P.a. LpxC	*Aquifex aeolicus* Deacetylase LpxC	37.1%	1P42	2.00
	AalpxcTU-514 Complex	37.1%	1XXE	NA
E. coli LpxC	TNSA, a catalytic component of the TN7 transposition system	23.1%	1F1Z	2.40
	Aquifex aeolicus Deacetylase LpxC	32.9%	1P42	2.00
	AalpxcTU-514 Complex	32.9%	1XXE	NA

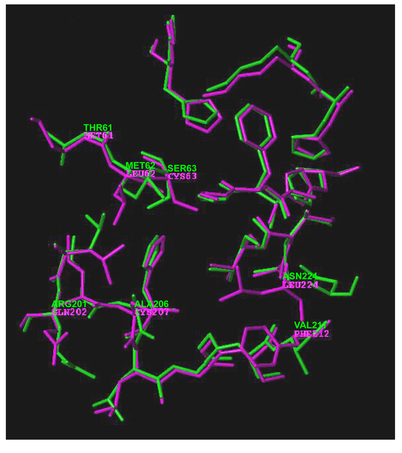
- Permutation selection of different loop candidates and side-chain rotamers
- Minimization of the models
- Addition of Zn^{2+} and water molecules

Topology of *E. coli* and *P. aeruginosa* LpxC



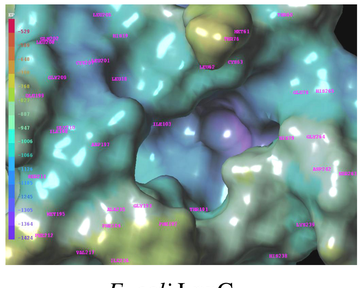
Structural topology of *E. coli* LpxC (a) and *P. aeruginosa* LpxC (b). α helices are colored red, β strands are colored green, cyan, yellow, and blue. N and C indicate the N-terminal and C-terminal regions of the protein.

E. coli LpxC-*P. aeruginosa* LpxC Active-Site Analysis

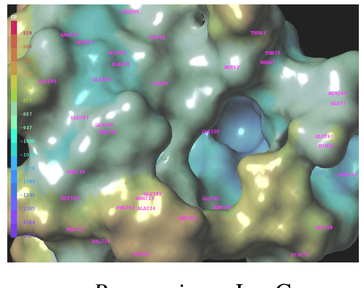


Active site residues of *E. coli* LpxC (magenta) superpositioned onto *P. aeruginosa* LpxC (green). The differences are highlighted by labelled residues in the picture.

MEP Surface Analysis



E. coli LpxC

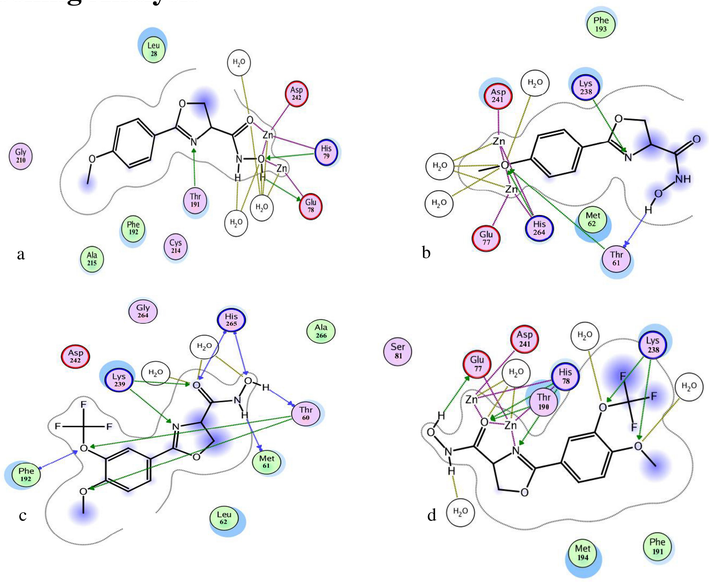


P. aeruginosa LpxC

Cavity Depth Analysis

Differences were observed in the cavity depths at the active site cleft near the Zn^{+2} binding pocket. *E. coli* LpxC presented a depth value of 4.4 to 5.2 Å whereas it was 4.7 to 6.3 Å for *P. aeruginosa* LpxC.

Docking Analysis



Selectively docked molecules in active sites of the homology models. Figures a & b indicate docking of *E. coli* inhibitor and c& d indicate docking of the *P. aeruginosa* inhibitor into the *E. coli* and *P. aeruginosa* LpxC resp.

Conclusions

- Reliable homology models of *E. coli* and *P. aeruginosa* LpxCs were created.
- Several minor but potentially important structural differences in the catalytic domains of the two proteins were identified. These differences could be responsible for variable activities of the inhibitors in the two proteins.
- The differences identified in this study might facilitate the design of inhibitors with broad-spectrum LpxC inhibitory activity

Publication

Kadam *et al*, J. Chem. Inf. Model., 2007, 47, 1215-1224

References

1) Young *et al*., J. Biol. Chem. 1995, 270, 30384-30391
2) Mdluli *et at*., Antimicrob. Agents Chemother, 2006, 50, 2178-2184