

## Supporting information

### Substrate specificity of OXA-48 after $\beta$ 5- $\beta$ 6 loop replacement.

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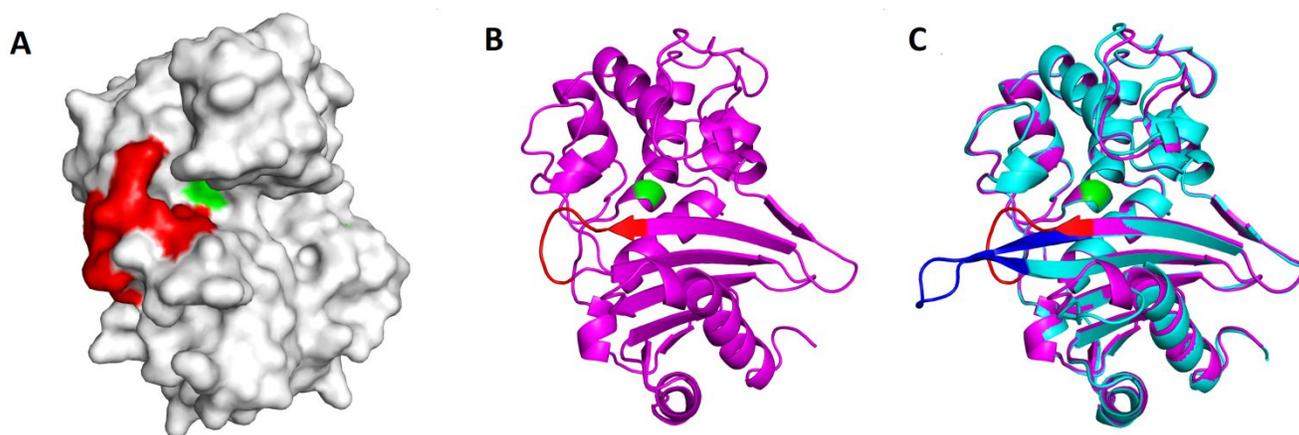
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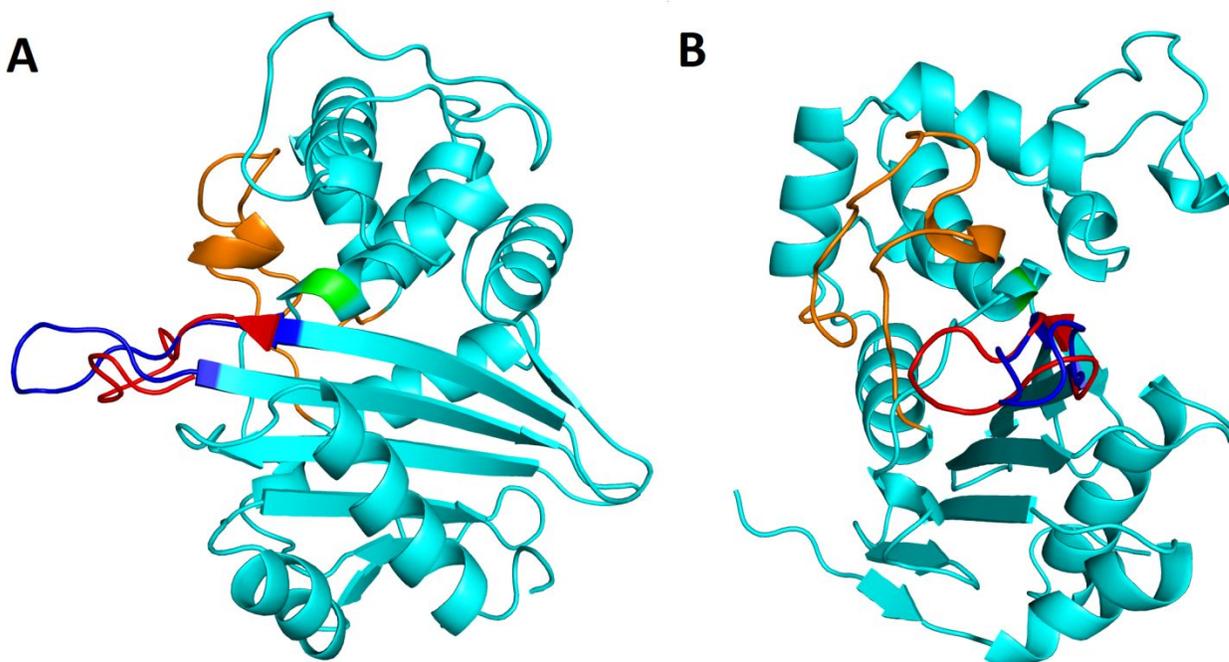
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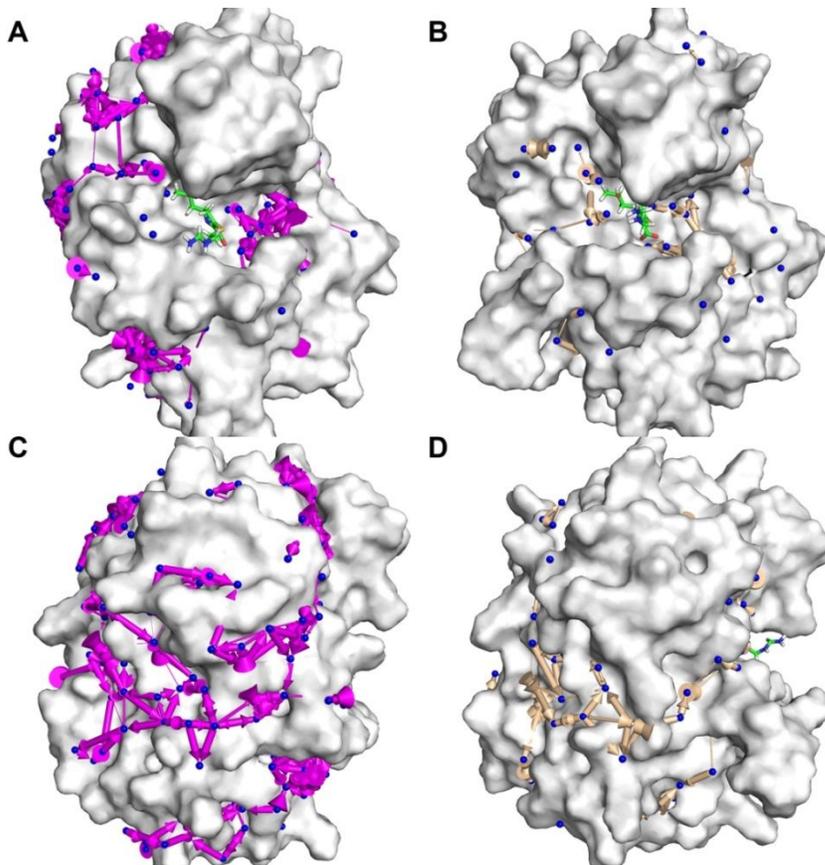
Figures S1 to S4



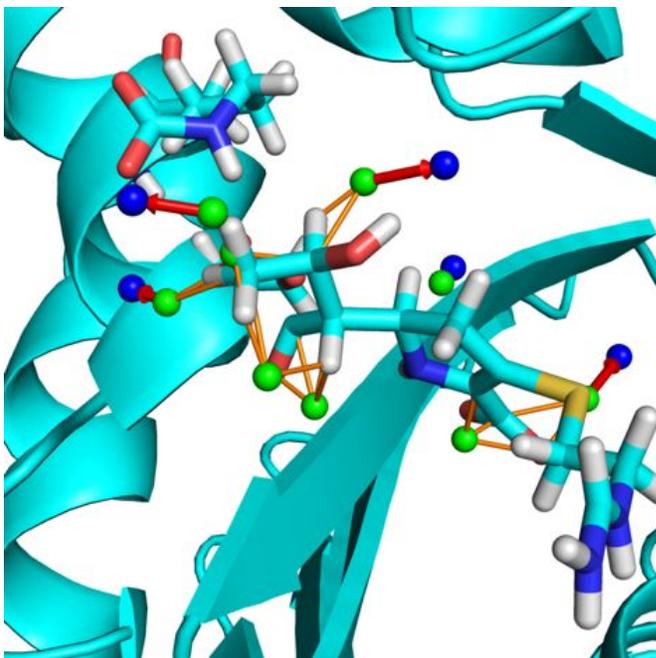
**Figure S1.** Structure of OXA-48 and  $\beta 5$ - $\beta 6$  loop replacement. Active site serine 70 is colored green and observed at the bottom of the active site cavity, for reference. A) Surface representation of OXA-48, showing the active site cavity wall formed by the  $\beta 5$ - $\beta 6$  loop, depicted in red. B) Backbone representation of OXA-48 showing the orientation of its  $\beta 5$ - $\beta 6$  loop. C) Backbone representation of OXA-48loop18 (cyan) superposed on OXA-48 (magenta), showing the difference in conformation of the replaced  $\beta 5$ - $\beta 6$  loop (red and blue for OXA-48 and OXA-48loop18, respectively).



**Figure S2.** Conformation of  $\beta 5$ - $\beta 6$  loop in OXA-48Loop18 crystal structure. Front view (A) and side view (B). Backbone representation of OXA-48loop18, colored cyan. For reference, active site serine 70 and  $\Omega$  loop, at the left of the active site, are colored green and orange, respectively. Chains A and B in the crystal structure of OXA-48Loop18 show their  $\beta 5$ - $\beta 6$  loops in a different orientation, with this loop extending away from the active site cavity in chain B (colored blue) and folding back towards the  $\Omega$  loop in chain A (colored red).



**Figure S3.** Water networks around OXA-48 and OXA-48Loop18 complexes with imipenem. Dynamic water networks around the protein surface, determined by HOP analysis. It shows the position where water molecules would interact with the protein surface, and how they are proposed to “jump” between positions. A) OXA-48/imipenem complex, front view. B) OXA-48Loop18/imipenem complex, front view. C) OXA-48/imipenem complex, back view. D) OXA-48Loop18/imipenem complex, back view. Notice the larger amount of conserved water sites obtained for OXA-48/imipenem simulations relative to OXA-48Loop18/imipenem.



**Figure S4.** Displacement of active site water molecules by imipenem. Conserved water molecule sites determined by HOP for simulations of OXA-48 (green spheres) and OXA-48-imipenem covalent complex (blue spheres). Overlaps displayed with orange lines. Notice the shift (red arrows) of certain water molecule sites caused by the presence of imipenem in the active site. Other water molecule binding positions are simply filled by the antibiotic, such as the oxyanion hole or the pocket for the C3 carboxylate.