What determines oxazolidinone binding to the large ribosomal subunit?

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The ribosome is an attractive target for antibiotics that inhibit protein synthesis by binding to the peptidyl transferase center (PTC) and exit tunnel of the large ribosomal subunit. Structural determination by X-ray crystallography only provides *static* views of the binding processes but does neither reveal the *dynamics* involved in antibiotics binding nor energetic determinants of binding. Computational approaches such as molecular dynamics (MD) simulations in combination with free energy calculations are suitable to fill this gap.

In the present study, we aim at investigating the determinants of binding of oxazolidinone antibiotics. This class is one of the only three new classes of synthetic antibiotics that have entered the market during the last 30 years especially for the treatment of Gram-positive infections. [1] In particular, we investigate linezolid, its derivative radezolid, and a structurally related oral anti-coagulant drug rivaroxaban in complex with the *H. marismortui* (H50S) archaeal structure. [2] The molecular mechanics adaptive Poisson Boltzmann surface area (MM-APBSA) method is used to determine the effective free energy of binding, also on a per-residue level. [3] Furthermore, we are investigating the influence of mutations that are not directly in contact with the ligand but still confer resistance to linezolid. [4]

The structural and energetic analysis identifies radezolid as better binder than linezolid, and rivaroxaban as a non-binder to the H50S subunit. As to the influence of mutations, we observe that a double mutant confers linezolid resistance, which is in concert with published data.

The information gained from this study provides insights into the binding of oxazolidinones to H50S and can be used to develop new oxazolidinone antibiotics rationally.

References

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