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Improvising docking protocols in searching for new small molecules that can inhibit the *Salmonella* ParE/Topoisomerase IV to overcome antibiotic-resistance.

Ravikiran S. Yedidi*
Department of Intramural research core, The Center for Advanced-Applied Biological Sciences & Entrepreneurship (TCABS-E), Visakhapatnam 530003, A.P. India. (*Correspondence to R.S.Y.: tcabse.india@gmail.com).

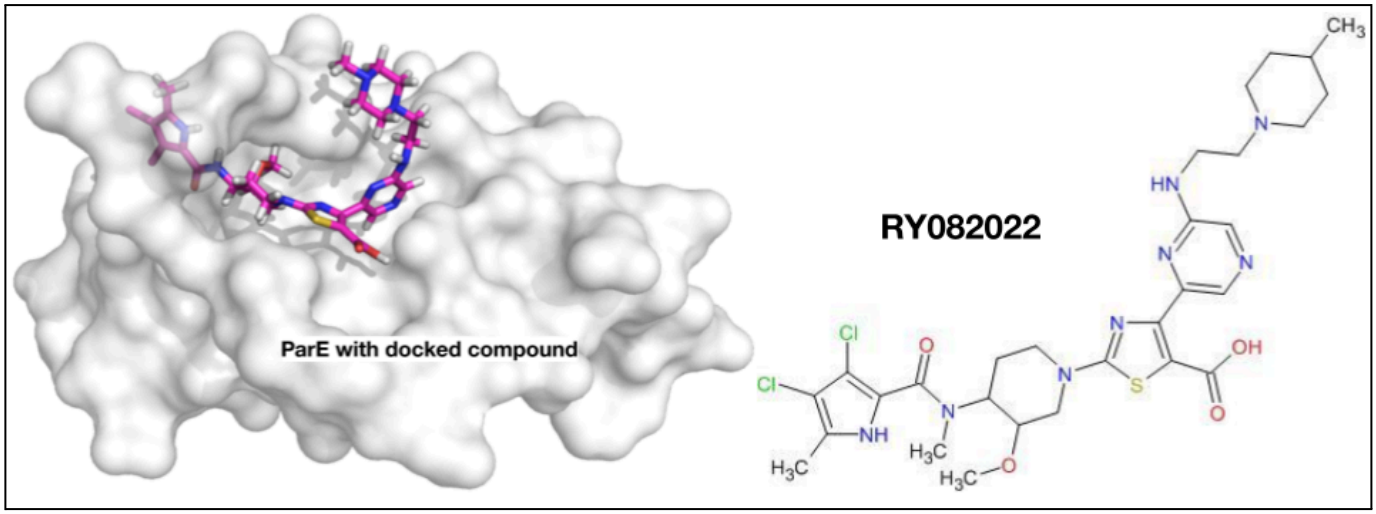

Figure 1. New compound, RY082022 docked against the *Salmonella* ParE protein.

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Antibiotics should often be used under the supervision of appropriate clinicians which would otherwise lead to multidrug-resistance [1]. Among the different classes of antibiotics that are available till date, the DNA gyrase or topoisomerase inhibitors that are derivatives of quinolones such as the ciprofloxacin, levofloxacin, etc. have been the most promising [2]. However, in the past decade many cases have been reported that show ciprofloxacin-resistance [3] suggesting that bacterial evolution under the clinical selection pressure continues and that humans must continue to design and evaluate new compounds to circumvent the antibiotic-resistance problem [4]. In search of new small molecules with potent antibiotic activity we need to extend our search for drug targets in parallel to the search for new antibiotic molecules [5]. Molecular docking protocols have been extensively utilized in the field of computer-aided drug design (CADD) [6]. Various *in silico* CADD protocols are used for designing and/or searching for a small molecule with good binding profile [7, 8] with the help of different open source and commercial docking software programs [9]. Recently we chose the ParE from *Salmonella Spp*. as the drug target and performed CADD by using various potent small molecule scaffolds that were previously reported [10].

Among the scaffolds that we tested, the pyrrolamide scaffold showed a new binding site on the ParE structure when docked with the hit compound, RY082022 (Figure 1). ParE was either considered alone as shown in Figure 1 or as a part of the DNA topoisomerase IV. The docking results gave a curved binding profile for RY082022 in line with its entropic features with extensive hydrogen bonding and van der Waals interactions. The binding affinity as calculated by the docking software was -9.11 kcal/mol. while the docking score of its parent scaffold was -8.24 kcal/mol. These results suggest that RY082022 certainly enhanced the overall binding affinity compared to its parent scaffold but whether it is active *in vitro* is yet to be tested. Currently we are in the process of molecular dynamics simulations-based analysis to confirm if improvising the molecular docking protocols for screening hit molecules against *Salmonella* ParE as a drug target would identify a new lead molecule towards the fight against the antibiotic-resistance.

Molecular docking is a versatile technique to identify hits against various drug targets either using the virtual screening protocols or structure-based drug-design. However, nothing can be finalized until proven using *in vitro* and/or *in vivo* experiments that support the *in silico* binding affinities. For example, the HIV-1 protease has been used as a drug target

for CADD and many compounds have been designed based on the substrate binding in the active site. In this case, the active site is a closed chemical space with not much variability unless one uses a mutant variant of the HIV-1 protease. In spite of a highly flexible structure with loops and flaps, a few angstroms of root mean square deviations (RMSDs) within the active site of the protease may not significantly affect the newly designed ligand as long as these RMSDs lie within the Luzzati errors of the protein structure. On the other hand, if the ligand binding site on the protein is not a completely closed chemical space then the entropic factors of both the receptor and ligand play a significant role in the ligand binding affinity when compared *in silico* vs. *in vitro*. Even though the HIV-1 protease contains a closed active site, amino acid substitutions within the active site cause clinical drug-resistance due to unusual structural deviations that alter the entropic behavior of the closed active site in HIV-1 protease [11]. Additionally, shallow binding pockets with high structural flexibility may lead to loss of ligand potency upon mutations in the receptors as commonly seen in the case of the hepatitis-C protease.

Typically in most of the cases people use rigid docking protocols where the 3-dimensional structure of the receptor is static i.e., even though if the ligand binding site is in a flexible region and not a closed chemical space, the ligand binding affinity can be high that can mislead in the scoring and ranking of the ligands screened. Any false positives that are identified in the docking protocols without proper manual evaluation can result in a ligand without any activity either *in vitro* or *in vivo*. RY082022 was identified to bind around a flexible loop within ParE with a binding affinity of -9.11 kcal/mol. This model has to be further simulated to test whether the entropic factors contributed by the flexible loop of ParE affect the binding affinity of RY082022. Molecular dynamics simulations involving the free energy perturbation protocols using molecular mechanics force fields can answer this question to some extent. However, until the molecule is synthesized and evaluated *in vitro* and *in vivo* it is hard to predict whether RY082022 can be a true lead compound for inhibiting the ParE activity. Furthermore, the bioavailability of the compound also plays a significantly high role in the context of reaching its therapeutic concentration at the site of action when consumed.

In conclusion, RY082022 is a small molecule identified via virtual screening from a library of compounds in the online databases that binds around a flexible loop of *Salmonella* ParE within a shallow binding pocket on the surface of the protein and is prone to large conformational changes of the flexible loop. In future, RY082022 will be synthesized and evaluated *in vitro* and *in vivo* in order to test its antibiotic potential to verify whether it can tolerate the flexible binding pocket on ParE without losing its binding affinity. Additionally, the pharmacological properties, ADME and toxicity of RY082022 should also be evaluated in future before proceeding to the human clinical trials.

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