Thermodynamic and structural insights into the inhibitors of SARS-CoV-2 main protease from repurposing drug libraries

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Although researchers have been working tirelessly since the COVID-19 outbreak, there is yet no effective drug found to directly treat the disease. Given the slow pace and substantial costs of new drug discovery and development, repurposing of existing drugs for the ongoing disease becomes an attractive proposition. In a recent study, a high-throughput x-ray crystallographic screen has been performed for the drugs which have been approved or are in clinical trials. 37 compounds have been identified from drug libraries, which bind to the SARS-CoV-2 main protease (3CLPro). Some of these compounds show antiviral activities, with reported effective concentrations that reduced SARS-CoV-2 infectious particles by 50% (EC50) in cell assay.

In the current study, we use molecular dynamics simulation and an ensemble-based free energy approach, namely, enhanced sampling of molecular dynamics with approximation of continuum solvent (ESMACS), to investigate a subset of the aforementioned compounds. 14 of the compounds are selected, which bind non-covalently to one of the three binding sites: the substrate-binding site, and the allosteric site I and II. Two sets of ESMACS simulations are performed, using individual x-ray structures for each of compounds or using the same protein structure for all of the compounds.

The drugs studied here are highly diverse, interacting with different binding sites and/or subsites of 3CLPro. The two sets of ESMACS simulations produce the same free energy predictions, within the error bars, for 12 out of 14 compounds. The protein structures are all very similar from x-ray crystallography, with a RMSD < 0.4 Å for the backbone atoms. The differences of the predicted free energies for the 2 compounds highlight the importance of the local conformations, of which side chains of some residues have different orientations at the binding site. ESMACS generates free energy rankings that are in excellent agreement with the experimental data derived from EC50 values. Our study also provides detailed chemical insight into the nature of drug-protein binding, which would shed light on the design and discovery of potential drugs.