

## **Small Molecule Interference with the hACE2 and SARS-CoV-2 RBD Complex Junction**

Camryn Carter, Justin Airas and Carol A. Parish

The continuation of the COVID-19 pandemic, caused by the global spread of SARS-CoV-2, has increased the need for antiviral solutions. In the current study, we analyzed the interactions of the SARS-CoV-2 receptor binding domain (RBD) with the human angiotensin-converting enzyme 2 (hACE2); and sought ways to disrupt that binding with repurposed small molecules. We used Schrödinger's Glide Docking to explore the conformational space of each ligand interacting at the RBD-hACE2 interface and used high-ranking docked poses as initial structures for subsequent long-time scale AMBER molecular dynamics. We examined the potential for ligand disruption of the RBD-hACE2 interaction using a variety of analyses, including MM-GBSA binding estimations, hydrogen bonding occurrence, percent dissociation, per residue binding analysis, and residue fluctuations. We find that of the ligands we screened, Fosinopril and Fosinoprilat are the most favorable for binding within the RBD-hACE2 interface. From our preliminary analysis we believe that the shared phosphinate groups are responsible for Fosinopril and Fosinoprilat's favorable interaction with the interface. We plan to exploit this structural relationship to design more effective SARS-CoV-2 inhibitors.