In silico Analysis of Small Molecules With Possible SARS-CoV-2 RNA-Dependent RNA Polymerase Inhibiting Properties and Their Therapeutic Potential

Yang, Michael (School: A&amp
M Consolidated High School)

Since an effective and reliable antiviral drug against COVID-19 (caused by the SARS-CoV-2 virus) has not been developed, research on novel therapeutic targets is crucial. The RdRp protein of SARS-CoV-2 was the perfect target because this protein is exclusive only to viruses while also being an extremely under-researched protein. An in silico project was optimal for examining the RdRp of SARS-CoV-2 as a therapeutic target. A library of synthetically-available small-molecule compounds was prepared, and virtual screening on the active site of SARS-CoV-2 RdRp using structure-based docking was performed. Several compounds proved to be bonded to the binding site of the RdRp with a uniquely low binding affinity. These compounds were further tested in vitro to determine the IC50 through enzyme assays. The binding of the small molecules onto the RdRp was also confirmed with binding assays. Ultimately, several molecules were found to clearly inhibit RNA production efficiently in the RdRp. Furthermore, of the compounds screened, several compounds belonged to a uniquely prevalent structural cluster, with a central amide linker connecting piperidine and indazole ring systems, which could possibly represent a novel class of COVID-19 inhibitors. With these data, future studies could conduct in vitro experiments to confirm this possible drug design, and lead to novel drugs to fight the COVID-19 global pandemic. Furthermore, these compounds could also apply to any virus that is structurally similar to SARS-CoV-2. The discovery of these novel COVID-19 inhibitors based on the RdRp of SARS-CoV-2 in silico and in vitro could also possess applications against novel diseases, therefore preventing the onslaught of another COVID-19-like pandemic.