Designing Novel Disruptors of SARS-CoV-2 Viral Spike Protein Function by Targeting the Nucleotide Binding Site of Chaperone Protein GRP78

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GRP78, a host auxiliary factor for many viruses, is a promising target for antiviral treatment of SARS-CoV-2 because of its role in forming a complex with ACE2 and the viral spike protein. Further studies have also shown that disrupting GRP78 function in vitro down-regulate ACE2 expression, leading to reduced viral cell entry. It is believed that binding to nucleotide binding domain (NBD) is responsible for disrupting GRP78 function, and compounds that capable of disrupting GRP78 function will serve as promising leads for the discovery of potential early-treatment options for SARS-CoV-2. After literature review completion and confirmation of GRP78 binding sites, we were able to choose appropriate databases in preparation to compute our own virtual screens. By comparing the nucleotide binding domain (NBD) residues used in different academic articles and available drugs repurposed to target the NBD of GRP78, we have determined the binding sites and residues. After a careful review of ZINC15 database, we decided to use the NIH, International Drug Collection, and ChEMBL as the final databases for docking to avoid those databases that have already been screened by other research groups. We first docked ATP to the NBD of 5E84 (ATP-bound state of GRP78) Chain A after we removed its original ligand ATP, as a control to make sure the docking site is specified correctly. Then, we have performed our own virtual screens by utilizing the software Glide to calculate docking-scoring grids for binding sites and conduct ligand docking. After docking, the most promising ligands were selected based on the information gathered from both previous literature and our own virtual screens. The top molecules have been determined based on their binding affinity compared to the control ligand ATP, as well as other ADME properties that are available for any in vivo or in vitro studies about their toxicity to human body. By using QikProp Software, we have determined the most promising ligands that have the highest binding affinity to GRP78 and the best ADME properties for orally and potentially intranasally delivered drugs. By discovering ligands that can successfully reduce the rate of SARS-CoV-2 spike protein binding to the human ACE2 receptor, this project will vastly advance the development of antiviral treatments and slow the escape evolution of the SARS-CoV-2 viral spike protein.