S protein

Entry of SARS-CoV-2 into human cells is dependent on the SARS-CoV receptor, angiotensin-converting enzyme 2 receptor, and cathepsin. Cathepsin degrades the spike protein (S protein), which results in the entry of viral nucleic acid into the human host cell.

The spike glycoprotein (S protein) of SARS-CoV-2 is a key target of antiviral drugs. Focusing on the existing S protein structure, molecular docking was used in this study to calculate the binding energy and interaction sites between 14 antiviral molecules with different structures and the SARS-CoV-2 S protein, and the potential drug candidates targeting the SARS-CoV-2 S protein were analyzed. Tizoxanide, dolutegravir, bictegravir, and arbidol were found to have high binding energies, and they effectively bind key sites of the S1 and S2 subunits, inhibiting the virus by causing conformational changes in S1 and S2 during the fusion of the S protein with host cells. Based on the interactions among the drug molecules, the S protein and the amino acid environment around the binding sites, rational structure-based optimization was performed using the molecular connection method and bioisosterism strategy to obtain Ti-2, BD-2, and Ar-3, which have much stronger binding ability to the S protein than the original molecules. This study provides valuable clues for identifying S protein inhibitor binding sites and the mechanism of the anti-SARS-CoV-2 effect as well as useful inspiration and help for the discovery and optimization of small molecule S protein inhibitors [1)].

1)
Sun C, Zhang J, Wei J, Zheng X, Zhao X, Fang Z, Xu D, Yuan H, Liu Y. Screening, simulation, and optimization design of small molecule inhibitors of the SARS-CoV-2 spike glycoprotein. PLoS One. 2021 Jan 25;16(1):e0245975. doi: 10.1371/journal.pone.0245975. PMID: 33493227; PMCID: PMC7833228.