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Relaxed complex scheme and molecular dynamics simulation suggests small molecule inhibitor of human TMPRSS2 for combating COVID-19

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Abstract

As the coronavirus disease 19 (COVID-19) pandemic continues to pose a health and economic crisis worldwide, the quest for drugs and/or vaccines against the virus continues. The human transmembrane protease serine 2 (TMPRSS2) has attracted attention as a target for drug discovery, as inhibition of its catalytic reaction would result in the inactivation of the proteolytic cleavage of the SARS-CoV-2 S protein. As a result, the inactivation prevents viral cell entry to the host's cell. In this work, we screened and identified two potent molecules that interact and inhibit the catalytic reaction by using computational approaches. Two docking screening experiments were performed utilizing the crystal structure and holo ensemble structure obtained from molecular dynamics in bound form. There is enhancement and sensitivity of docking results to the holo ensemble as compared to the crystal structure. Compound 1 demonstrated a similar inhibition value to nafamostat by interacting with catalytic triad residues His296 and Ser441, thereby disrupting the already established hydrogen bond interaction. The stability of the ligand–TMPRSS2 complexes was studied by molecular dynamics simulation, and the binding energy was re-scored by using molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) binding free energy. The obtained compounds may serve as an initial point toward the discovery of potent TMPRSS2 inhibitors upon further in vivo validation.

Keywords

COVID-19; SARS-COV-2; Virtual screening; Molecular dynamics; Ensemble structure