Fragment Based Drug Discovery of SARS-CoV-2 Main Protease

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SARS-CoV-2, known as severe acute respiratory syndrome coronavirus 2, is a new type of coronavirus responsible for 2019 pandemic of COVID-19. SARS-CoV-2 main protease (M^{pro}), also a 3C-like cysteine protease ($3CL^{pro}$), is one of the key enzymes of coronaviruses and plays a crucial role in mediating viral replication and transcription. Five non-covalent ligands were designed and grown for Southampton 3C-like protease (SV3CP) based on a hit from crystal-based fragment screening. These five ligands were crystalised with SARS-CoV-2 M^{pro} because of the similar active sites shared by SV3CP and SARS-CoV-2 M^{pro}, and we determined crystal structures of SARS-CoV-2 M^{pro} in complex with two ligands (S04 & S05). SARS-CoV-2 M^{pro} in complex with S05 is shown in **Figure 1**. We also developed a kinetic assay specific to SARS-CoV-2 M^{pro} showing Ki values of these five ligands range from 9.3 μM to 0.87 mM. These ligands show their potential as broad spectrum drug leads due to their inhibition activity in different 3CL proteases.

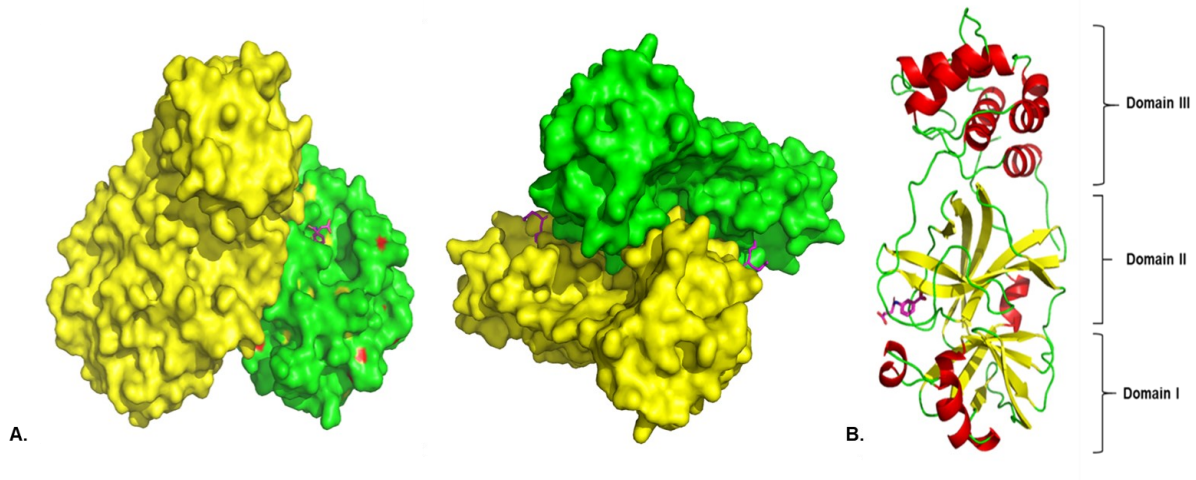

Figure 1. Structure of SARS-CoV-2 M^{pro} in complex with Ligand S05. A. Surface representation of the homodimer of SARS-CoV-2 M^{pro} in complex with S05. B. One protomer in complex with S05 (magenta).

Keywords:SARS-CoV-2 M^{pro}; X-ray crystallography; 3C-like protease; Drug discovery; Kinetic assay.