Investigating Novel Thiazolyl-Indazole Derivatives as Scaffolds for SARS-Cov-2 M^{Pro} Inhibitors

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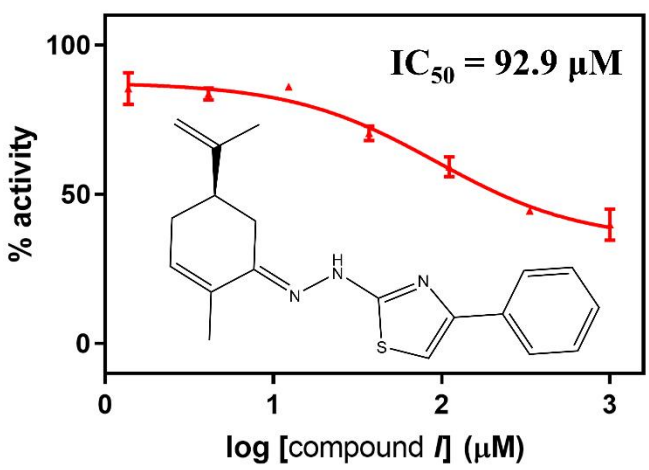

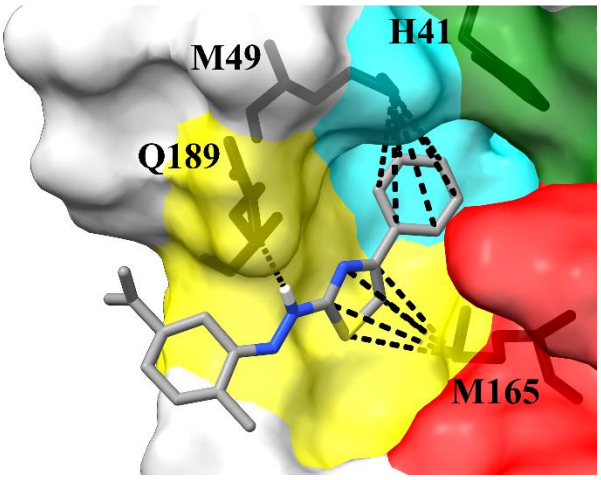

COVID-19 is a global pandemic caused by infection with SARS-CoV-2. Remdesivir, a SARS-CoV-2 RNA polymerase inhibitor, is the only drug to have received widespread approval for treatment of COVID-19. The SARS-CoV-2 main protease enzyme (M^{Pro}), essential for viral replication and transcription, remains an active target in the search for new treatments. In this study, the ability of novel thiazolyl-indazole derivatives to inhibit M^{Pro} is evaluated. The binding affinity and atomistic interactions of each compound were evaluated through Schrödinger Glide Docking, AMBER molecular dynamics simulations, and MM-GBSA free energy estimation. These results were compared with similar calculations of M^{Pro} binding various 5-mer substrates (VKLQA, VKLQS, VKLQG). From these simulations, we can see that binding is driven by residue specific interactions such as π-stacking with His41, and S/π interactions with Met49 and Met165. The compounds were also experimentally evaluated in a M^{Pro} biochemical assay and the most potent compound containing a phenylthiazole moiety inhibited protease activity with an IC_{50} of 92.9 µM. This suggests that the phenylthiazole scaffold is a promising candidate for the development of future M^{Pro} inhibitors.