Integrative discovery of SARS-CoV-2 Mpro inhibitors through virtual screening and in vitro validation

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In this comprehensive study, we delineate an integrative strategy to inhibit the SARS-CoV-2 main protease (Mpro), a critical enzyme in the viral replication cycle, using a synergy of computational and experimental techniques. Initially, we developed and validated ligand-based pharmacophore models, which served as a basis for the virtual screening of extensive chemical libraries, intending to identify potent Mpro inhibitors. The screening process yielded promising candidates which were subjected to rigorous molecular dynamics simulations. These simulations provided deep insights into the binding dynamics and stability of the inhibitor-Mpro interactions, enabling the refinement of compound selection based on their predicted efficacy and binding affinity. Following computational analyses, compounds with the highest potential were advanced for in vitro validation. These assays confirmed the inhibitory activity of selected compounds against the SARS-CoV-2 Mpro, with some showing significant efficacy in impeding viral replication. Moreover, the study also explored the structure-activity relationships (SAR) of these compounds, providing valuable insights into the molecular determinants of inhibitor efficacy and laying the groundwork for further optimization. This research embodies a paradigm shift in antiviral drug discovery, highlighting the power of combining virtual screening and molecular dynamics simulations with empirical validation to expedite the identification of therapeutic candidates. By offering a detailed exploration of the molecular interactions between inhibitors and the SARS-CoV-2 Mpro, our study not only identifies potential leads for COVID-19 treatment but also sets a precedent for the rapid development of antiviral therapies against future pandemic threats.