Computer-aided drug design and screening of potential compounds to combat COVID-19

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SARS-CoV-2 causes the current global pandemic coronavirus disease 2019. Widely-available effective drugs could be a critical factor in halting the pandemic. The main protease ($3CL^{pro}$) plays a vital role in viral replication; therefore, it is of great interest to find inhibitors for this enzyme. We applied the combination of virtual screening based on molecular docking derived from the crystal structure of the peptidomimetic inhibitors (N3, 13b, and 11a), and experimental verification revealed FDA-approved drugs that could inhibit the $3CL^{pro}$ of SARS-CoV-2. Three drugs were selected using the binding energy criteria and subsequently performed the $3CL^{pro}$ inhibition by enzyme-based assay. In addition, six common drugs were also chosen to study the $3CL^{pro}$ inhibition. Among these compounds, lapatinib showed high efficiency of $3CL^{pro}$ inhibition (IC_{50} value of 35 ± 1 μM and K_i of 23 ± 1 μM). The binding behavior of lapatinib against $3CL^{pro}$ was elucidated by molecular dynamics simulations. This drug could well bind with $3CL^{pro}$ residues in the five subsites S1', S1, S2, S3, and S4. Moreover, lapatinib's key chemical pharmacophore features toward SAR-CoV-2 $3CL^{pro}$ shared important HBD and HBA with potent peptidomimetic inhibitors. The rational design of lapatinib was subsequently carried out using the obtained results. Our discovery provides an effective repurposed drug and its newly designed analogs to inhibit SARS-CoV-2 $3CL^{pro}$. Besides the known drugs, biochemical and cell-based assays tested the screened compounds from natural products and synthetic analogs.