Ligand-Based Design, and Molecular Dynamics of Small Molecules as Possible M^{pro} Inhibitors

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Abstract:

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been the scope of recent studies worldwide to control its pandemic. Given the similarity with the earlier SARS-CoV, it is possible to use the previously reported inhibitors to develop a new treatment for the current attack of SARS-CoV-2. This study used the formerly published SARS-CoV Mpro small-molecule protease inhibitors to develop a pharmacophore model in order to design new ligands. Several strategies and scaffolds were evaluated in-silico giving rise to ten newly designed compounds. Molecular docking and dynamics simulation were performed on Mpro enzyme in its active site to evaluate the newly designed ligands I-X. The results obtained from this work showed that compounds III- VI had better molecular docking score than the co-crystallized ligand baicalein (3WL) giving -5.99, -5.94, -6.31, -6.56 and -5.74 Kcal/mol, respectively. Moreover, they could bind to Mpro binding site better than I, II and VII-X. The most promising chromen-2-one based compounds V-VI proved acceptable physicochemical and ADMET properties to be considered new leads for further investigations. This new understanding should help to improve predictions of the impact of new treatment on COVID-19.