In silico Design and Synthesis Planning of Potential Nucleoside Inhibitors of SARS-CoV-2 RNA-Dependent RNA polymerase (RdRp)

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiological agent of COVID-19, is a novel virus that causes mild to severe respiratory tract infections. One of the desired protein targets in discovering possible antiviral drugs for COVID-19 is the RNA-dependent RNA polymerase (RdRp). The said enzyme is responsible for the viral replication machinery, whereby inhibiting this enzyme may lead to a low viral count in the host cell. In this study, particular compounds of interest are nucleoside derivatives. Those compounds may inhibit the replication process by mimicking the binding of the substrate (nucleoside triphosphate) at the active site of the target enzyme. Pocket-based analysis from the molecular dynamics simulations was used to assess other possible pockets at the RdRp wherein proposed nucleoside derivatives can have significant molecular interaction. Also, molecular docking studies and 3D Quantitative Structure-Activity Relationship (3D-QSAR) analysis were employed to propose potential nucleoside drugs with enhanced binding energy and interaction towards the RdRp probed pockets. Finally, the designed compounds were then synthesized, wherein MIT ASKCOS and IBM RXN were utilized to optimize the synthesis route of proposed nucleoside derivatives. The drug design strategy employed in this study aims to promote a time-efficient framework for discovering antiviral drugs against COVID-19 and future pandemics.

Keywords: COVID-19, SARS-COV-2 RNA-dependent RNA polymerase, nucleoside derivatives, drug design