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Original article

Computational studies on potential new anti-Covid-19 agents with a multi-target mode of action

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ABSTRACT

A compound that could inhibit multiple targets associated with SARS-CoV-2 infection would prove to be a drug of choice against the virus. Human receptor-ACE2, receptor binding domain (RBD) of SARS-CoV-2 S-protein, Papain-like protein of SARS-CoV-2 (PLpro), reverse transcriptase of SARS-CoV-2 (RdRp) were chosen for in silico study. A set of previously synthesized compounds (**1**–**5**) were docked into the active sites of the targets. Based on the docking score, ligand efficiency, binding free energy, and dissociation constants for a definite conformational position of the ligand, inhibitory potentials of the compounds were measured. The stability of the protein–ligand (P-L) complex was validated *in silico* by using molecular dynamics simulations using the YASARA suit. Moreover, the pharmacokinetic properties, FMO and NBO analysis were performed for ranking the potentiality of the compounds as drug. The geometry optimizations and electronic structures were investigated using DFT. As per the study, compound-**5** has the best binding affinity against all four targets. Moreover, compounds 1, 3 and 5 are less toxic and can be considered for oral consumption.

1. Introduction

Covid-19 caused by SARS-CoV-2, was first reported from China on December 2019. Since then, the virus has been rapidly spreading around the whole world and has become a global pandemic (Mohapatra et al., 2020; Mohapatra et al., 2021a, 2021b). Initial infection control measures (e.g. quarantine, lockdown, and the use of masks) implemented to tackle the high transmission rate of the virus proved beneficial. These steps, however, are not sufficient on their own to control the spread of this rapidly-mutating virus. SARS-CoV-2 variants, including B.1.351 (SA), B.1.1.7 (UK), B.1.427, B.1.429 (USA), B.1.617.2 (India), and B.1.1.529 (South

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