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Molecular modelling and structure-activity relationship of a natural derivative of *o*-hydroxybenzoate as a potent inhibitor of dual NSP3 and NSP12 of SARS-CoV-2: *in silico* study

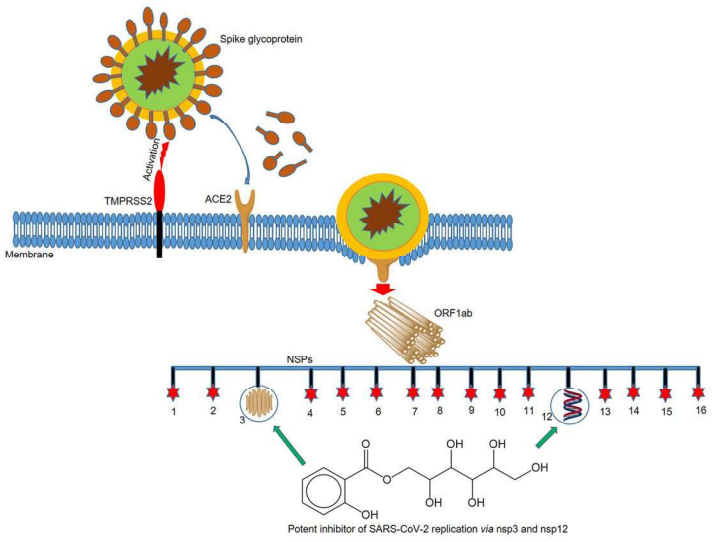
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ABSTRACT

The nsp3 macrodomain and nsp12 (RdRp) enzymes are strongly implicated in the virulent regulation of the host immune response and viral replication of SARS-CoV-2, making them plausible therapeutic targets for mitigating infectivity. Remdesivir remains the only FDA-approved small-molecule inhibitor of the nsp12 in clinical conditions while none has been approved yet for the nsp3 macrodomain. In this study, 69,067 natural compounds from the IBScreen database were screened for efficacious potentials with mechanistic multitarget-directed inhibitory pharmacology against the dual targets using *in silico* approaches. Standard and extra precision (SP and XP) Maestro glide docking analyses were employed to evaluate their inhibitory interactions against the enzymes. Four compounds, STOCK1N-45901, 03804, 83408, 08377 consistently showed high XP scores against the respective targets and interacted strongly with pharmacologically essential amino acid and RNA residues, in better terms than the standard, co-crystallized inhibitors, GS-441524 and remdesivir. Further assessments through the predictions of ADMET and mutagenicity distinguished STOCK1N-45901, a natural derivative of *o*-hydroxybenzoate as the most promising candidate. The ligand maintained a good conformational and thermodynamic stability in complex with the enzymes throughout the trajectories of 100 ns molecular dynamics, indicated by RMSD, RMSF and radius of gyration plots. Its binding free energy, MM-GBSA was recorded as –54.24 and –31.77 kcal/mol against the respective enzyme, while its structure-activity relationships confer high probabilities as active antiviral, anti-inflammatory, antiinfection, antitussive and peroxidase inhibitor. The IBScreen database natural product, STOCK1N-45901 (2,3,4,5,6-pentahydroxyhexyl *o*-hydroxybenzoate) is thus recommended as a potent inhibitor of dual nsp3 and nsp12 of SARS-CoV-2 for further study.



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