Computational repurposing of asthma drugs as potential inhibitors of SARS-CoV-2 M^{pro}

A. Hussain[1] **and A. Hussain**[2]

1) *Department of Bioinformatics, Maulana Azad National Institute of Technology, Bhopal, 462003 and* 2) *Rajasthan Technical University, Kota, 324010, India*

Keywords: Asthma drugs, COVID-19, drug repurposing, molecular docking, SARS-CoV-2
Original Submission: 2 September 2021; **Revised Submission:** 26 March 2022; **Accepted:** 1 April 2022
Article published online: 11 April 2022

Corresponding author: A. Hussain.
E-mail: ahussain591@gmail.com

Dear Editor

COVID-19, a new viral pneumonia, was initially discovered in China and expanded rapidly throughout the world. COVID-19 had affected over 472,816,657 as of March 23, 2022, as shown in a WHO press release, with over 6,099,380 deaths. The rate of infection and numbers of deaths continues to rise, and no verified medications or authorized new drugs have so far been discovered. As a result, the progress of an anti-COVID-19 had become a worldwide health crisis. The main protease (M^{pro}) of the COVID-19 virus is liable for the proteolysis of replicase polyproteins, as a result of development of a variety of functional proteins required for viral replication as well as transcription [1]. The dearth of directly linked homologues in humans, as well as $M^{pro's}$ functional importance in the viral life cycle, makes it an interesting target for antiviral medicines [2]. Even though multiple articles on SARS-CoV M^{pro} have been published, no protease new inhibitor has yet to move to the preclinical stage. Since then, researchers have shown a unique X-ray structure of SARS-CoV-2 M^{pro} in conjunction including reversible dipeptide inhibitor X77. Even so, to our understanding, this final crystal structure was never used for virtual drug database screening against asthma drugs. According to a study from Oxford University, early treatment with the asthma drug budesonide can diminish the serious risk of rigorous SARS-CoV-2 illness and shorten the time to recovery. There are presently no specific target drugs available, and effective therapy alternatives are limited [3]. Reportedly, there is no medication for COVID-19, and research into the infection's therapy, particularly vaccines, is currently in progress. Remdesivir and ritonavir are two clinical candidates which have obtained a lot more attention [4]. Even though it was specifically introduced as a stand-alone antiviral, it was shown to be effective when used in combination with low-dose ritonavir and also other protease inhibitors. As a result, the process of discovering new antiviral drugs is extremely difficult, costly, and time-consuming. Screening existing compounds intended for COVID-19 therapy is an appealing strategy for rapidly identifying highly promising drug candidates with already-optimized pharmacokinetics and minimal toxic side effects [5]. Therefore, computer-aided drug design (CADD) procedures have been identified as a viable solution. Structure-based virtual screening (SBVS) utilizing molecular docking study has conclusively demonstrated to be a very excellent technique for antiviral and antibacterial drug development becoming an important starting point in the finding of new lead compounds for the treatment of various diseases. SBVS was used in this research on asthma drugs. The Schrödinger software suite was used to define a docking framework against the target protein. The goal is to develop novel SARS-CoV-2 major protease (M^{pro}) inhibitors with high binding interaction in the binding site as well as binding pocket stability. This study aimed to discover potential inhibitors of COVID-19's main protease using a compounds screening, followed by ADMET and MMGBSA assessment to discover novel inhibitors that could be used as potential leads for medicating coronavirus infections.

The COVID-19 disease harmed everyday life. One in every five people in the world is thought to be at greater risk for developing severe COVID-19 infection due to underlying health issues. Repurposing existing medications could be a great way to reach therapeutic interventions demonstrated to be safe and effective in clinical trials. We identified asthma medications that can be powerful inhibitors of the COVID-19 M^{pro} on the basis of molecular compounds with their docking score presented in Table 1. Asthma drugs **vilanterol** and **salmeterol** attach to the COVID-19 main protease's active site and shown tight interaction than the reference ligand X77 and the drug budesonide (studied by Oxford University). The docking score of vilanterol (-8.727) and salmeterol (-8.635) is also high than X77

https://doi.org/10.1016/j.nmni.2022.100979

TABLE 1. 2D structure representation of the asthma drugs with reference compound, following respective docking scores

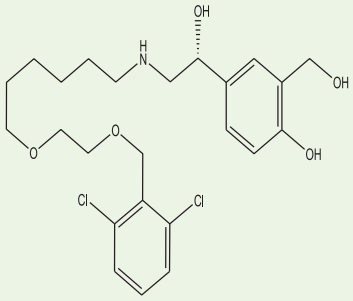
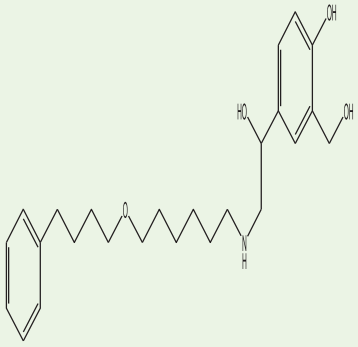
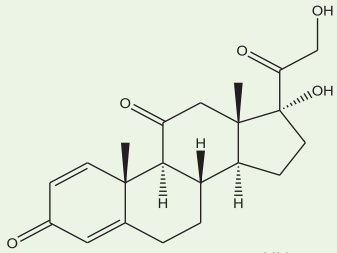
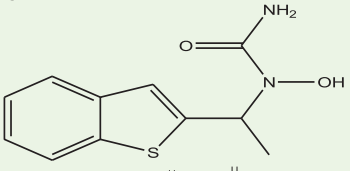
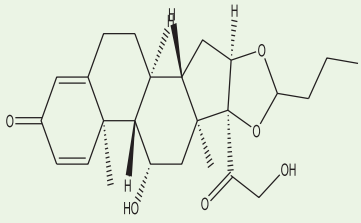
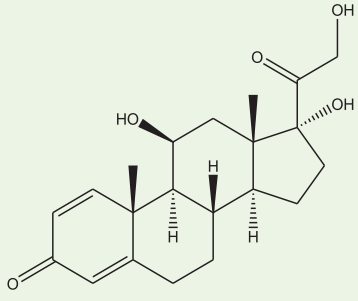
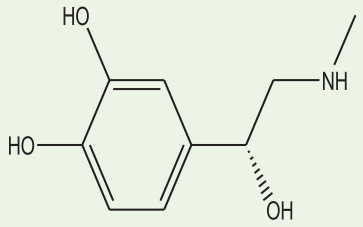
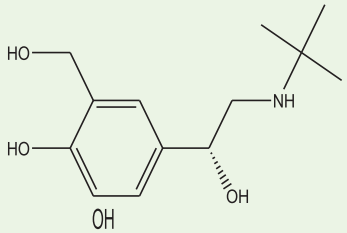
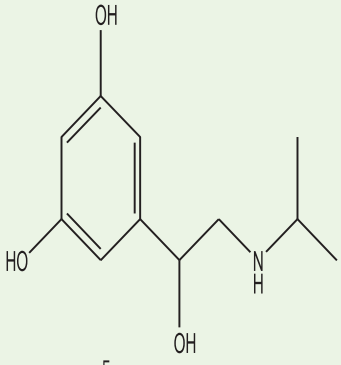
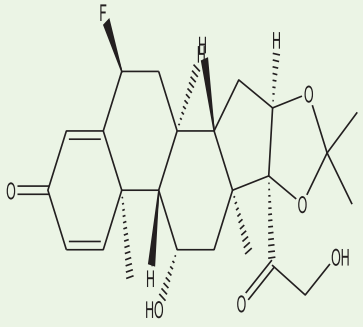
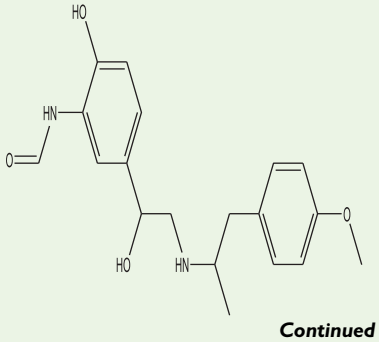
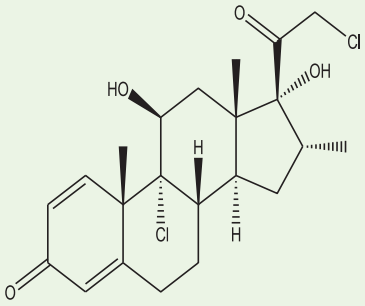
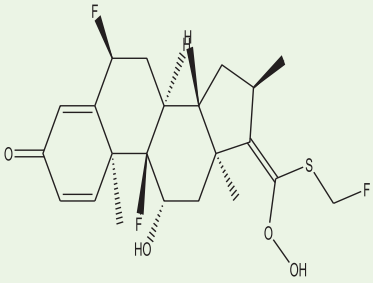
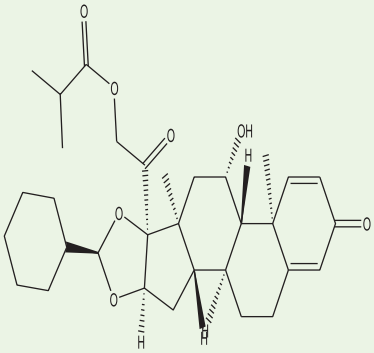
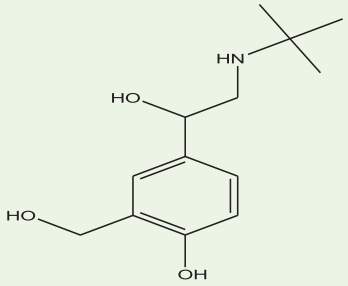
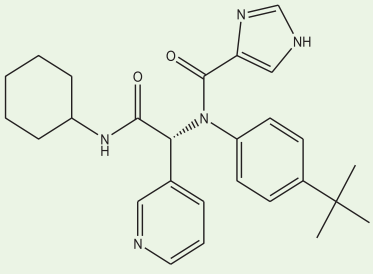
S. No.	Compound name	Mol. formula	Mol. Wt.	Docking score	2d structure
1	Vilanterol	C24H33Cl2NO5	486.43	-8.727	
2	Salmeterol	C25H37NO4	415.56	-8.635	
3	Prednisone	C21H26O5	358.42	-6.618	
4	Zileuton	C11H12N2O2S	236.29	-6.430	
5	Budesonide	C25H34O6	430.53	-6.077	
6	Prednisolone	C21H28O5	360.44	-6.045	

TABLE 1. Continued

S. No.	Compound name	Mol. formula	Mol. Wt.	Docking score	2d structure
7	Epinephrine	C9H13NO3	183.20	-5.685	
8	Levalbuterol	C13H21NO3	239.31	-5.587	
9	Metaproterenol	C11H17NO3	211.25	-5.154	
10	Flunisolide	C24H31FO6	434.49	-5.055	
11	Formoterol	C19H24N2O4	344.40	-4.756	

Continued

TABLE 1. Continued

S. No.	Compound name	Mol. formula	Mol. Wt.	Docking score	2d structure
12	Mometasone	C22H28Cl2O4	427.36	-4.643	
13	Fluticasone	C22H27F3O4S	444.51	-4.638	
14	Ciclesonide	C32H44O7	540.69	-4.358	
15	Albuterol	C13H21NO3	239.31	-2.264	
—	X77[r] r = Reference compound	C27H33N5O2	459.58	-7.640	

(-7.640) and drug budesonide (-6.077). As a result, these drug candidates could be promising anti-COVID M^{pro} agents. However, to confirm inhibition activity, these drugs must be evaluated using in-vitro methods.

Transparency declaration

The authors declares no conflict of interest.

Funding and acknowledgements

The authors want to acknowledge the Department of Bioinformatics, MANIT, for providing the research facility to complete the research work. They are also thankful to the Schrodinger team for providing the software facility.

References

[1] Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2021;19(3):141–54.
[2] Liu YC, Kuo RL, Shih SR. COVID-19: the first documented coronavirus pandemic in history. Biomed J 2020;43(4):328–33.
[3] Jean SS, Lee PI, Hsueh PR. Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 2020;53(3):436–43.
[4] Vitiello A, Ferrara F. Remdesivir versus ritonavir/lopinavir in COVID-19 patients. Irish J Med Sci 2021;190(3):1249–50.
[5] Gaudêncio SP, Pereira F. A computer-aided drug design approach to predict marine drug-like leads for SARS-CoV-2 main protease inhibition. Marine Drugs 2020;18(12).