

Molecular Docking Analysis of Anti-Severe Acute Respiratory Syndrome-Coronavirus 2 Ligands against Spike Glycoprotein and the 3-Chymotrypsin-Like Protease

Abstract

Background: The severe acute respiratory syndrome-like disease coronavirus disease 2019 (COVID-19) is a disastrous global pandemic with 16,288,490 infected cases and 649,884 deaths. Until now, no effective treatments are found. **Methods:** The virus uses the 3-chymotrypsin-like protease for inducing the activity of the viral polyproteins and the spike (S) glycoprotein for human cell entry through the human angiotensin-converting enzyme 2 receptor. Blocking the active binding sites of these molecules might be beneficial for decreasing the activity of the virus and suppressing the viral entry to the human cells. Here, docking methods were used to identify a group of ligands may perform the blocking operations. **Results:** The results revealed the strongest binding affinities, sorted high to low, for tadalafil (Cialis) (phosphodiesterase type 5 inhibitor, tirofiban (antiplatelet), paraxanthine (central nervous system stimulant), dexamethasone, gentian violet cation (triphenylmethane), salbutamol, and amlodipine (calcium channel blocker). **Conclusion:** These substances may provide vital help for further clinical investigation in fighting against the current global pandemic of the COVID-19.

Keywords: *Cialis, coronavirus disease 2019, dexamethasone, ligands, salbutamol, severe acute respiratory syndrome-coronavirus 2*

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Introduction

The coronavirus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic continues to generate high numbers of infected cases and deaths around the globe, which currently passed 16,288,490 infections and 649,884 deaths.^[1] It started in Wuhan, Hubei province, China, in the last quarter of the year 2019.^[2] This virus, as currently hypothesized, originated in bats due to using those animals for human food consumption, as indicated by the first cases appeared in the seafood and wet markets in Wuhan.^[3] Scientists all worldwide have launched numerous studies to understand the structural characteristics of the virus in attempts to find a suitable treatment.^[4,5]

The virus uses human angiotensin-converting enzyme 2 (hACE2) receptor to perform its entry to the human cells. This fact was unveiled by sequence-studying

the virus genetic materials, which demonstrated a strong similarity with the SARS-CoV.^[6,7] The risk of infection possibility by the SARS-CoV-2 to humans is higher than that of the SARS-CoV. This might be due to the high affinity of the virus for the hACE2 receptor. This was proven by using a HeLa cell-line expressed with hACE2 and infected with SARS-CoV-2 and SARS-CoV.^[7,8] The coronaviruses, in general, need the spike (S) glycoprotein to bind to the hACE2 receptor using certain domains called S^B.^[9-14] This fact was thoroughly demonstrated for the SARS-CoV-2, revealing that the virus uses S^B domain of the S glycoprotein to enter the human cells through the hACE2 receptor.^[15] The latest authors provided crystallographic structures of the S glycoprotein (closed and open-ectodomain-trimer states). The coronaviruses utilize another machinery component called 3-chymotrypsin-like protease (3CL^{pro}), which cleaves 11 sites in different proteins of the virus. This action converts those proteins into functional

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elements on the induction of viral replication. Some of these viral proteins are RNA-dependent RNA polymerase, a single-stranded RNA-binding protein, a helicase, an exoribonuclease, an endoribonuclease, and a 2'-O-ribose methyltransferase.^[16] The 3CL^{Pro} could be a therapeutic target by using suitable ligands to block the protease binding site.

Blocking the active binding sites of these molecules might be beneficial for decreasing the activity of the virus and suppressing the viral entry to the human cells. Here, docking methods were utilized to identify a group of ligands that may perform the blocking operations.

Methods

A number of ligands (some of the food and drug administration [FDA] approved drugs), [Table 1], were used to targets active sites of the SARS-CoV-2 S glycoprotein (closed, RCSBPDBID: 6 vxx, and partially open, RCSBPDBID: 6 vyb, states) and the 3CL^{Pro}, RCSBPDBID: 6 LU7, after removing the ligand using PyMOL^[17] using PyRx-Python Prescription (0.8) with employing Autodock plugin^[18] and PyMOL.^[17] For the target sites of the S glycoprotein, the S^B domain was employed as described by Walls *et al.*^[16] for the closed and open states. For the 3CL^{Pro} sites, the binding pocket residues; HIS41, MET49, CYS145, HIS163, GLU166, and HIS172, were targeted.^[19,20] Intermolecular distances between the ligands and amino acids of the viral targets were described in 3-dimensional (3D) model images generated by Discovery Studio Visualizer v20.1.0.19295 (BIOVIA, Dassault Systemes BIOVIA, Paris, France). Silico studies could provide insightful information about details of the complicated biological systems, in which molecular docking could specifically describe the mechanistic of ligand-target interactions for the purposes of drug design.^[21-23]

Results

The findings, [Table 2], revealed high affinity values of the used ligands with the highest in tadalafil (Cialis), tadalafil, paraxanthine, dexamethasone, gentian violet cation, salbutamol, and amlodipine.

Table 1: Ligands used in the protein docking and their PubChem IDs

PubChem CID	Ligand
110635	Tadalafil
145708838	Tirofiban
4687	Paraxanthine
5743	Dexamethasone
3468	Gentian violet cation
2083	Salbutamol
2162	Amlodipine
439544	N, N'-Diacetylchitobiose
84265	N-Acetyl-2-deoxy-2-amino-galactose
644170	2-(Acetylamino)-2-deoxy-alpha-D-mannopyranose

Table 2 autodock binding affinity values of ligands to the S glycoprotein (closed and open states) and 3CL^{Pro}.

For the closed state of the SARS-CoV-2 S glycoprotein, the 3D exploring of the hACE2 binding sites, S^B, showed adjacent attachment pockets of the selected ligand molecules, tadalafil, tirofiban, and gentian violet cation, on the surface of the viral protein, [Figure 1].

Regarding the open state of the SARS-CoV-2 S glycoprotein, the 3D poses of the ligand binding revealed similar sitting pockets in the S^B partially open ectodomain of the protein when tadalafil, dexamethasone, and gentian violet cation were used in the current session, [Figure 2].

In the case of the SARS-CoV-2 3CL^{Pro}, the 3D searching of the ligand affinity for binding with the enzyme demonstrated close-by regions for this binding for both tadalafil and dexamethasone in the pocket defined by the HIS41, MET49, CYS145, HIS163, GLU166, and HIS172 active binding residues of the viral protein, [Figure 3]. For the intermolecular distances between the ligand and amino acids, [Figures 4-6] show these distances in details for the closed and open structures of the spike protein and the 3CL^{Pro}, respectively.

Discussion

Although SARS-CoV-2 (COVID-19) has a less fatality potential comparing to other deadly diseases, such as Marburg virus, Ebola, Crimean-Congo hemorrhagic fever, or HIV, the novel CoV is way far different due to its high level of transmission. This uniqueness rises up due to the disease nature as a respiratory disease in which transmission occurs via the patient's respiratory expelled fluids by sneezing and coughing. Second, no innate immunity is present as the virus newly emerged, due to the mishandling of wild animals, bats as most recognized. Third, the disease is thought to be with a high occurrence rate, 17.9%, of asymptomatic infections that increases the chances of transmission in a tremendous way.^[24] Moreover, the virus seems to mostly attack elderlies or people with underlying health conditions, such as cardiovascular, blood hypertension, diabetes, and cancer issues, and about 50% of these individuals become critically ill and need respiration enhancements in intensive care units.^[25] The answer to this puzzling tropism is the overexpression of angiotensin-converting enzyme 2 receptor in the lungs of those patients who have heavy demands on the renin-angiotensin system.^[26]

The idea of the docking based work, here, is to block the activity of viral proteins; S glycoprotein and 3CL^{Pro}. Here, the study tested the binding affinity of 10 ligands on these macromolecules. The findings unveiled that tadalafil, commercially known as Cialis, was with a high-kcl/mol-binding value when investigated on the S glycoprotein (closed and open states) and the 3CL^{Pro}. Tadalafil is a phosphodiesterase type 5 inhibitor (PDE5)

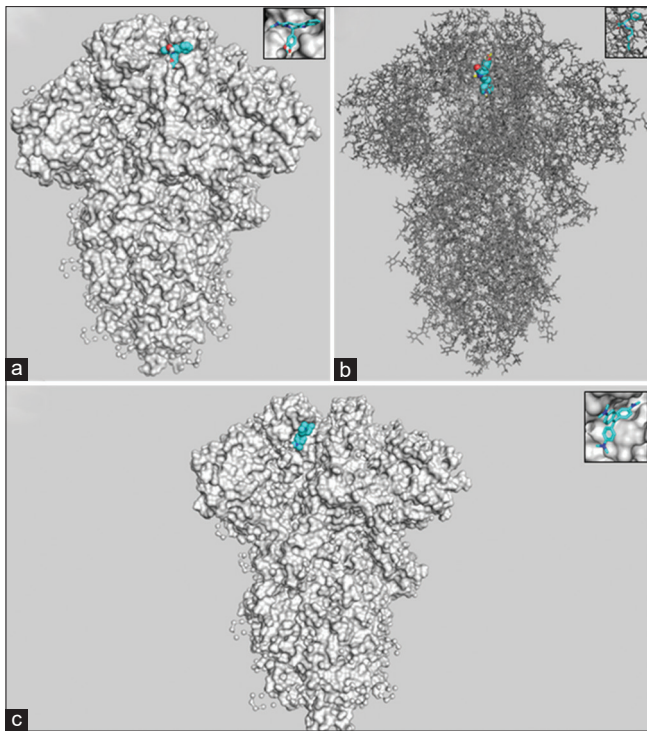


Figure 1: Images of the severe acute respiratory syndrome-coronavirus 2 spike glycoprotein (closed state, grey) with the ligands (blue); (a) Tadalafil. (b) Tirofiban. (c) Gentian violet cation. The binding of the ligands is displayed in the human angiotensin converting enzyme 2 binding sites, S⁸, of the viral protein

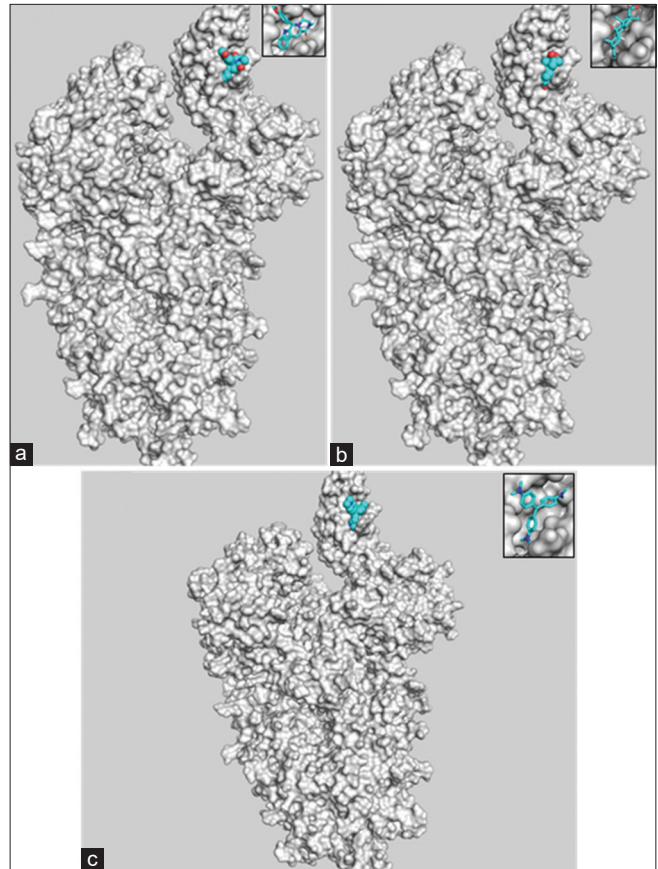


Figure 2: Images of the severe acute respiratory syndrome-coronavirus 2 spike glycoprotein (partially open, grey) with the ligands (blue); (a) Tadalafil. (b) Dexamethasone. (c) Gentian violet cation. The binding of the ligands is displayed in the human angiotensin converting enzyme 2 binding sites, S⁸, of the viral protein

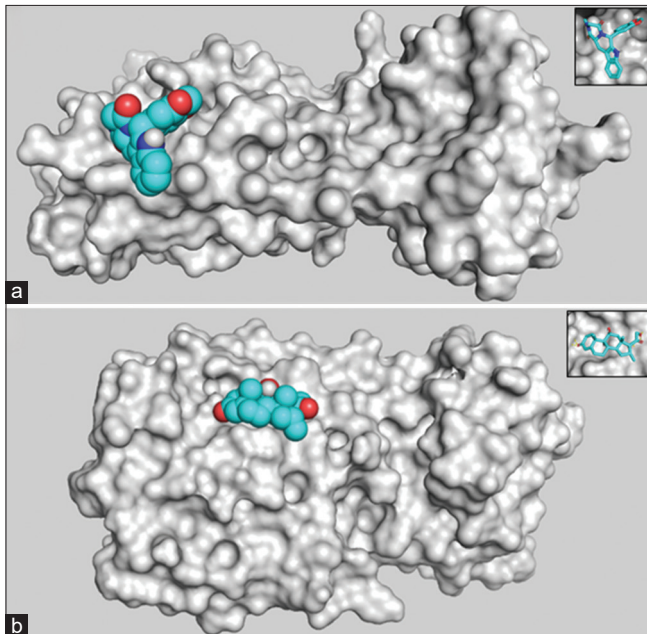


Figure 3: Images of the severe acute respiratory syndrome -coronavirus 2 3-chymotrypsin-like protease (gray) with the ligands (blue); (a) Tadalafil. (b) Dexamethasone. The binding of the ligands is displayed in the pocket sites of the HIS41, MET49, CYS145, HIS163, GLU166, and HIS172 active binding residues of the viral protein

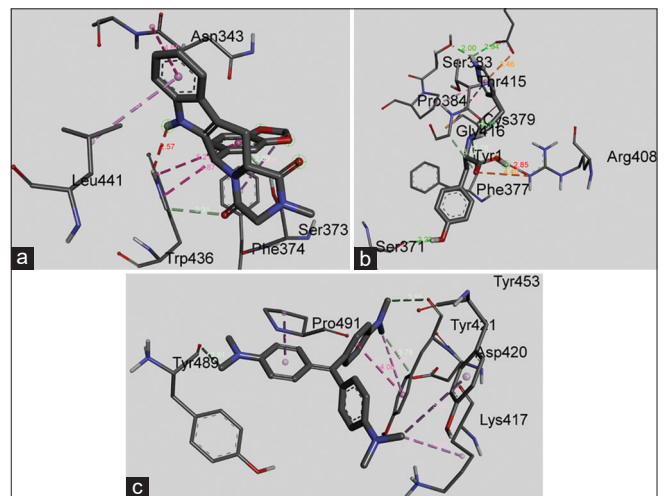


Figure 4: Intermolecular distances between the ligands and the amino acids of the severe acute respiratory syndrome-coronavirus 2 spike glycoprotein (closed state); (a) Tadalafil. (b) Tirofiban. (c) Gentian violet cation. The binding of the ligands is displayed in the human angiotensin-converting enzyme 2 binding sites, S⁸, of the viral protein

inhibitor used to treat erectile dysfunction.^[27] Nitric oxide (NO) generated by the neuronal NO synthase initiates erection, which is maintained by endothelial NO synthase

during erection stimulation. Later, NO stimulates guanylyl cyclase production that leads to the induction of the cyclic guanosine monophosphate (cGMP). Briefly, the increases

in the cGMP levels decrease calcium channel activity and eventually reduce the concentration of cytosolic calcium, which results in smooth muscle relaxation. The PDE5 breaks down the cGMP in the penis, encouraging erectile dysfunction, which can be reversed by the use of the PDE5 inhibitors.^[27-30] In addition to its common use, tadalafil is utilized in the treatment of class II and III pulmonary arterial hypertension. This disease condition is characterized by increases in both pulmonary vascular resistance and mean pulmonary arterial pressure by inhibiting the PDE5 enzyme.^[31] The findings of the current study could be further investigated in the treatment of the COVID-19.

Tirofiban, a glycoprotein IIb/IIIa receptor globally used medicine for the treatment of coronary artery disease due to its ability to reduce platelet aggregation, was found here to have high binding affinity to the closed state of the SARS-CoV-2 S glycoprotein through the hACE2 binding site on the viral protein.^[32] This may open the gate for

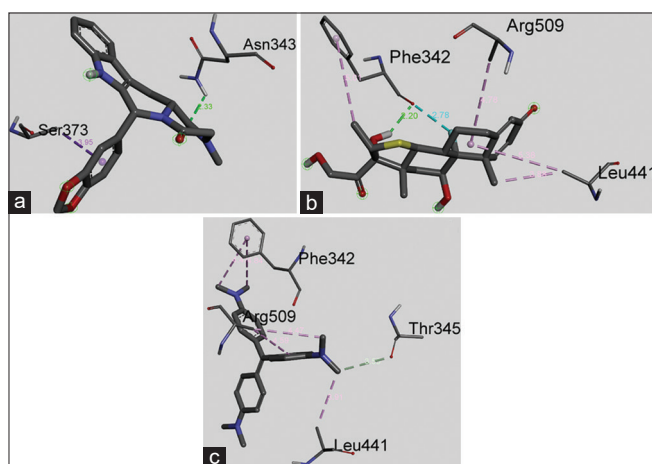


Figure 5: Intermolecular distances between the ligands and the amino acids of the severe acute respiratory syndrome-coronavirus 2 spike glycoprotein (partially open); (a) Tadalafil. (b) Dexamethasone. (c) Gentian violet cation. The binding of the ligands is displayed in the human angiotensin converting enzyme 2 binding sites, S^B, of the viral protein

more in-depth investigation about its curability against COVID-19; although, it might not be useful for patients with existed low blood clotting problems or injuries in certain body sites, internally or externally.

Interestingly, gentian violet cation was revealed in the present docking exploration to have high binding ability to the closed and ectodomain-open states of the S glycoprotein of the novel CoV. The gentian violet is known to generate antibacterial and antifungal activities. It was revealed by Bakker *et al.*^[33] to have greater anti-cutaneous *Candida*, anti-*Streptococcus*, and anti-*Staphylococcus* with low concentrations. The concept for this action is not well-understood; however, different explanations were introduced such as redox alterations, low-level nicotinamide adenine dinucleotides phosphate

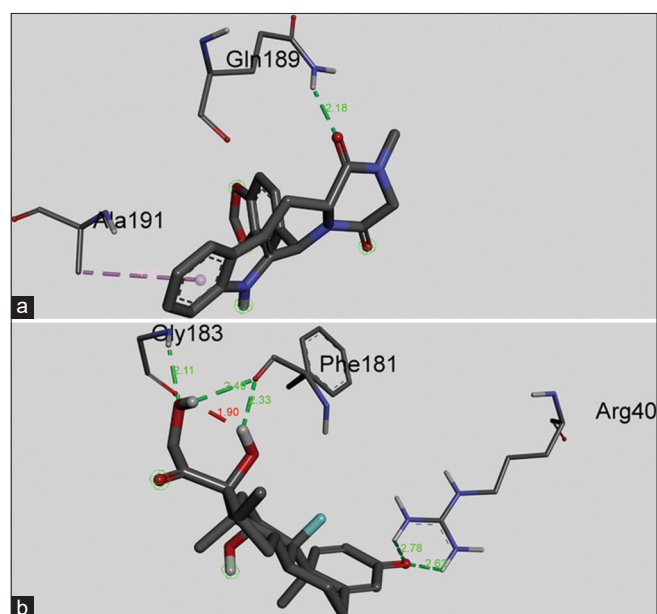


Figure 6: Intermolecular distances between the ligands and the amino acids of the severe acute respiratory syndrome-coronavirus 2 3-chymotrypsin-like protease; (a) Tadalafil. (b) Dexamethasone

Table 2: Autodock binding affinity values of ligands to the S glycoprotein (closed and open states) and 3-chymotrypsin-like protease

Ligand	Binding affinity values (kcal/mol)		
	S glycoprotein state		3CL ^{pro}
	Closed	Open	
Tadalafil	-8.5	-8.7	-5.9
Tirofiban	-7.5	-5.6	-5.2
Paraxanthine	-6.3	-5.7	-4.7
Dexamethasone	-6.9	-7.7	-6.4
Gentian violet cation	-6.8	-7.4	-5.3
Salbutamol	-6.1	-6.5	-4.8
Amlodipine	-5.5	-6.0	-5.2
N, N'-Diacetylchitobiose	-7.2	-6.9	-5.6
N-Acetyl-2-deoxy-2-amino-galactose	-6.1	-4.7	-4.9
2-(Acetylamino)-2-deoxy-alpha-D-mannopyranose	-6.1	-5.3	-4.9

oxidase inhibition, generation of free radicals, un-ionized complex production, suppression in protein synthesis and cell wall, decrease in glutamine synthesis, and oxidative phosphorylation uncoupling.^[34] It has been uncovered that gentian violet was highly effective in the treatment of oral hairy leukoplakia, a common oral HIV-patient condition with white plaques on the tongue edges due to Epstein–Barr virus.^[35] Furthermore, Aljofan *et al.*^[36] detected that gentian violet was potently able to *in-vitro*-defeat Nipah and Hendra viruses. Furthermore, gentian violet has a vital history in the systemic use as blood transfusion sterilizer in South Africa to prevent blood-borne diseases such as Chagas disease.^[34] A gentian violet analog, imipramine blue (imipramine-CID_3696), was constructed to fight certain systemic tumor cases.^[37,38] The present study found that this analog showed similar binding affinity values as in the gentian violet (data not shown).

Surprisingly, dexamethasone showed high values of binding affinity, especially with the open state of the SARS-CoV-2 S glycoprotein. This medicine is highly used in the treatment of many conditions, such as autoimmune diseases, allergies, or asthma. It was found that dexamethasone was able to reduce the production of mucus due to respiratory syncytial virus; however, no alteration in the antiviral interferon signaling was seen as a side effect of the use of dexamethasone.^[39] This may allow for the safe use of anti-COVID-19 treatment without a reduction in immunity directed against the virus. Interestingly, the current study revealed that almost all the used ligands showed attachment at the same pockets in the viral protein, which may indicate an active hotspot for the virus to perform its infectivity.

Conclusion

The current work provides a group of available ligands, some with FDA approved usage for certain conditions, to be virtually successful in the treatment of COVID-19. Interestingly, tadalafil and tirifiban reveal high binding activities to the spike protein of the virus. The current findings need further investigation *in vitro* and *in vivo* to complete the utilization approval for the current novel CoV pandemic.

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Conflicts of interest

There are no conflicts of interest.

References

1. Worldometer. Coronavirus Cases. Worldometer; 2020. p. 1-22. Available from: <https://www.worldometers.info/coronavirus/coronavirus-cases/#daily-cases>. [Last accessed on 2020 Apr 04].
2. Singhal T. A review of coronavirus disease-2019 (COVID-19). *Indian J Pediat* 2020;87:281.
3. Mackenzie JS, Smith DW. COVID-19: A novel zoonotic disease caused by a coronavirus from China: What we know and what we don't. *Microbiol Aust* 2020;41:45.
4. Mirzaei M, Harismah K, Da'I M, Salarzaei E, Roshandel Z. Screening efficacy of available HIV protease inhibitors on COVID-19 protease. *Mil Med* 2020;22:100-7.
5. Harismah KM. Favipiravir: Structural analysis and activity against COVID-19. *Adv J Chem B* 2020;2:55-60.
6. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, *et al.* A new coronavirus associated with human respiratory disease in China. *Nature* 2020;579:265-9.
7. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 2020;395:565-74.
8. Chen Y, Guo Y, Pan Y, Zhao ZJ. Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun* 2020;525:135-40.
9. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, *et al.* Identification of a novel coronavirus causing severe pneumonia in human: A descriptive study. *Chin Med J (Engl)* 2020;133:1015-24.
10. Yang XL, Hu B, Wang B, Wang MN, Zhang Q, Zhang W, *et al.* Isolation and characterization of a novel bat coronavirus closely related to the direct progenitor of severe acute respiratory syndrome coronavirus. *Virology* 2015;90:3253-6.
11. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS Pathog* 2018;14:e1007236.
12. Li W, Moore MJ, Vaslielva N, Sui J, Wong SK, Berne MA, *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003;426:450-4.
13. Li F, Li W, Farzan M, Harrison SC. Structural biology: Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. *Science (80-)* 2005;309:1864-8.
14. Kirchdoerfer RN, Wang N, Pallesen J, Wrapp D, Turner HL, Cottrell CA, *et al.* Erratum to: Stabilized coronavirus spikes are resistant to conformational changes induced by receptor recognition or proteolysis. *Sci Rep* 2018;8:15701.
15. Ge XY, Li JL, Yang X Lou, Chmura AA, Zhu G, Epstein JH, *et al.* Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* 2013;503:535-8.
16. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. *Cell* 2020;181:281-292.e6.
17. Thiel V, Ivanov KA, Putics Á, Hertzog T, Schelle B, Bayer S, *et al.* Mechanisms and enzymes involved in SARS coronavirus genome expression. *J General Virol* 2003;84:2305-15.
18. The PyMOL Molecular Graphics System. No Title. Schrödinger, LLC.; 2020. Available from: <https://pymol.org>. [Last accessed on 2020 Jul 27].
19. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Methods Mol Biol* 2015;1263:243-50.
20. Macchiagodena M, Pagliai M, Procacci P. Inhibition of the Main Protease 3CL-pro of the Coronavirus Disease 19 via Structure-Based Ligand Design and Molecular Modeling; 2020. Available from: <http://arxiv.org/abs/2002.09937>. [Last accessed on 2020 Apr 04].
21. Mirzaei. M. Science and engineering *in silico*. *Adv J Sci Eng*

- 2020;1:1-2.
22. Abyar Ghamsari P, Samadzadeh MM. Cytidine derivatives as inhibitors of methyltransferase enzyme. *Eurasian Chem Commun* 2019;1:310-17.
 23. Alidoosti ZS. Comparative examination of moclobemide, tranlycypromine, phenelzine and isocarboxazid for monoamine oxidase-a inhibition. *Adv Chem B* 2019;1:23-8.
 24. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill* 2020;25:2000180.
 25. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, evaluation and treatment coronavirus (COVID-19). *StatPearls* 202. NCBI Bookshelf ID: NBK554776 PMID: 32150360.
 26. Aronson JK, Ferner RE. Drugs and the renin-angiotensin system in covid-19. *BMJ* 2020;369:m1313.
 27. Coward RM, Carson CC. Tadalafil in the Treatment of Erectile Dysfunction. *Ther Clin Risk Manag* 2008;4:1315-30.
 28. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. *Urol Clin North Am* 2005;32:379-95.
 29. Carson CC. Phosphodiesterase Type 5 inhibitors: State of the therapeutic class. *Urol Clin North Am* 2007;32:507-15.
 30. Hurt KJ, Musicki B, Palese MA, Crone JK, Becker RE, Moriarity JL, *et al.* Akt-dependent phosphorylation of endothelial nitric-oxide synthase mediates penile erection. *Proc Natl Acad Sci U S A* 2002;99:4061-6.
 31. Henrie AM, Nawarskas JJ, Anderson JR. Clinical utility of tadalafil in the treatment of pulmonary arterial hypertension: An evidence-based review. *Core Evid* 2015;10:99-109.
 32. Juwana YB, Suryapranata H, Ottervanger JP, Van'T Hof AW. Tirofiban for myocardial infarction. *Expert Opinion Pharmacother* 2010;34:861-6.
 33. Bakker P, Van Doorne H, Gooskens V, Wieringa NF. Activity of gentian violet and brilliant green against some microorganisms associated with skin infection. *Int J Dermatol* 1992;31:210-3.
 34. Maley AM, Arbiser JL. Gentian violet: A 19th Century Drug Re-emerges in the 21st Century. *Exp Dermatol* 2013;22:775-80.
 35. Bhandarkar SS, MacKelfresh J, Fried L, Arbiser JL. Targeted therapy of oral hairy leukoplakia with gentian violet. *Am Acad Dermatol* 2008;58:711-2.
 36. Aljofan M, Sganga ML, Lo MK, Rootes CL, Porotto M, Meyer AG, *et al.* Antiviral activity of gliotoxin, gentian violet and brilliant green against Nipah and Hendra virus *in vitro*. *Virology* 2009;6:187.
 37. Munson J, Bonner M, Fried L, Hofmekler J, Arbiser J, Bellamkonda R. Identifying new small molecule anti-invasive compounds for glioma treatment. *Cell Cycle* 2013;12:2200-9.
 38. Munson JM, Fried L, Rowson SA, Bonner MY, Karumbaiah L, Diaz B, *et al.* Anti-invasive adjuvant therapy with imipramine blue enhances chemotherapeutic efficacy against glioma. *Sci Transl Med* 2012;4:127ra36.
 39. McAllister CS, Ansaldi D, Growcott EJ, Zhong Y, Quackenbush D, Wolff KC, *et al.* Dexamethasone inhibits respiratory syncytial virus-driven mucus production while increasing viral replication without altering antiviral interferon signaling. *Virology* 2020;540:195-206.

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