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# Repurposing of Anthelmintic Drugs against SARS-CoV-2 (Mpro and RdRp): Novel Disease, Older Therapeutics

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**Abstract:** Since late December 2019, the entire nations are facing the novel enemy of COVID-19, which has imposed a tremendous burden on the researchers across the globe to develop a treatment for it. Recognition of main protease and RNA dependent RNA polymerases as a promising target of SARS-CoV-2 encouraged us to repurpose some older antihelmintic drugs against COVID-19. In this constructive research, we have investigated anthelmintic drugs' antiviral activity, including ivermectin, doramectin, and selamectin, for their antiviral potential against SARS-CoV-2 by employing *in silico* tools. The selected drugs, including ivermectin, doramectin, and selamectin, were encountered as potential inhibitors of SARS-CoV-2 RNA-dependent RNA polymerases with an affinity of -9.2, -10.0, and -10.2 kcal/mol. They were found to exhibit main protease inhibitor activity with an affinity of -8.3, -8.7, and -9.0, respectively. Thus, using the repurposing approach in conjugation within *silico* tools, we have proposed ivermectin, doramectin, and selamectin as potential antivirals against SARS-CoV-2.

**Keywords:** COVID-19; anthelmintic drugs; RNA dependent RNA polymerases; main protease; *in silico* tools.



## 1. Introduction

The entire era faces the outbreak of pandemic COVID 19, which was previously recognized under the term of pneumonia invading in China's areas, especially in Wuhan, in late December 2019 [1–3]. SARS-CoV strain is recognized as frightful among the coronavirus producing massive deaths after spreading across nearly all the nations [4]. Similar to SARS-CoV, MERS-CoV emerged in Saudi Arabia and has about 2,500 cases, with 800 deaths [5]. The common clinical manifestations of COVID-19 include respiratory complications, fever, dry cough, muscle ache, and malaise [6]. World Health Organization declares COVID-19 as pandemic on 11 March 2020, which is ruinous for across the entire nations [7]. As of 26 August 2020, there has been 2,12,94,845 cases of COVID-19 are reported worldwide, along with more than 7,61,779 deaths all over the nations (Coronavirus Outbreak. Available at https://www.worldometers. info/coronavirus/). The developed countries, including the USA, Spain, and Italy, are suffering from the extreme death rate, which is rapidly increasing (Coronavirus Outbreak. Available at https://www.worldometers. info/coronavirus/). The

transmission of coronavirus among the population of various nations can be classified in four phases. Wherever the public transmission phase is tremendously dreadful and which causes healthcare system failure owing to a sudden unexpected increase in the number of cases which cannot be treated due to unavailability of an operative drug or vaccine against COVID-19 (COVID-19 Explainer: Four Stages of Virus Transmission, and What Stage India Currently Finds Itself In (https://weather.com/en-IN/india/coronavirus/news/2020-04-09- four-stages-of-virus-transmission-stage-India-currently-finds)).

Due to the extreme spread of COVID-19 across the globe, researchers and scientists worldwide are engaged in developing specific therapeutic drug candidates or vaccines against this pandemic disease. The currently available therapeutics for COVID-19 act as support, lacking specificity [10]. Various targets are being explored to design and develop potential therapeutic agents to fight against COVID-19, which involves angiotensin-converting enzyme-2 (ACE2) [11–13], COVID-19 main protease [14], RNA dependent RNA polymerase (RdRp) [15,16]. In our previous research, we have emphasized the SARS-CoV-2 and investigated several natural products and antiretroviral drugs exhibiting antiviral activity against SARS-CoV-2 [17,18]

Recently, the health care professionals in Bangladesh, claiming that ivermectin, an anthelmintic drug along with doxycycline, a tetracycline antibiotic, can help in combating COVID-19 (Bangladesh Medical Team Claims Ivermectin With Doxycycline Clears COVID-19. Available at https://worldhealth.net/news/bangladesh-medical-team-claims-ivermectin-doxycycline-clears-covid-19/). Tetracyclines, including doxycycline, suggested to exhibit potential in the management of COVID-19 [20]. Ivermectin is already reported to exhibit antiviral activities against a variety of infectious viruses, including pseudorabies virus (PSV), Dengue virus (DENV1-4) [21], human immunodeficiency virus-1 (HIV1), West Nile Virus, influenza, and Venezuelan equine encephalitis virus (VEEV) [21]. Several studies suggest that ivermectin, an anthelmintic drug as a potential candidate for the treatment of SARS-CoV-2 by exploring its *in vitro* examination [21–23]. In a Vero-hSLAM cell culture, in 48 hours, it is reported to exhibit around ~5000 fold decline in a viral population [21]. The mechanism of these drugs to possess potential towards COVID-19 is still unknown. Thus, we have explored ivermectin's potential along with other anthelmintic such as doramectin and selamectin by utilizing molecular docking studies with the promising targets of SARS-CoV-2, including main protease (Mpro) and RNA dependent RNA polymerase (RdRp).

## 2. Materials and Methods

The structures of drugs (ligands), including ivermectin, doramectin, and selamectin, were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and drawn in ChemDraw Ultra 12.0 [24]. The ligand structures were transformed into the most stable conformations utilizing the Vega ZZ program using the method of conjugate gradient and SP4 force field [25]. The final ligand preparation was done using AutoDock Tools 1.5.6 and saved in pdbqt format [26].

The 3D structure of the protein, including COVID-19 main protease in complex with an inhibitor N3 [27] (PDB ID: 6LU7) and SARS-CoV-2 RNA-dependent RNA polymerase [16] (PDB ID: 7BTF) were obtained from protein data bank (http://www.rcsb.org/pdb/home/home.do) and saved in PDB format. The active sites of respective proteins were determined using Discovery Studio Visualizer 4.0 program. The protein was prepared using AutoDock Tools 1.5.6 by removing water molecules, adding polar

hydrogen, and Kollman charges. The grid box was placed in the center of the protein structure using the auto grid method, and the x, y, z coordinates were saved. The protein structure was exported in pdbqt format. The ligands and proteins' final docking and proteins were performed by utilizing AutoDock Vina 1.0 at exhaustiveness of 80 [28]. The docking results were simulated and visualized in Discovery Studio Visualizer 4.0 and Pymol 1.8.6.0 [29]. The drug candidates were also screened for prediction of activity spectra for substances (PASS) in terms of probability of activity (Pa) and inactivity (Pi) values using the PASS online tool to propose probable therapeutic activities of the selected drug candidates [30].

## 3. Results and Discussion

The prediction of active sites presents in the binding pocket of proteins revealed various amino acids associated with the ligand. The predicted active site of both the target protein, including COVID-19 main protease in complex with an inhibitor N3 and SARS-CoV-2 RNA-dependent RNA polymerase, is shown in Figure 1 and Figure 2, respectively. The docking affinity score and PASS data, and 2D structure of the selected drug candidates are shown in Table 1. The post-docking analysis was represented in the form of the best-docked pose of the ligand in the protein's pocket. The amino acid residues attribute in ligand-protein interactions are depicted in Figure 3 Figure 4. The binding characterized by hydrogen bonds and hydrophobic interaction of the selected drugs and the amino acid residues and distance associated with the interactions is shown in Table 2 and Table 3.

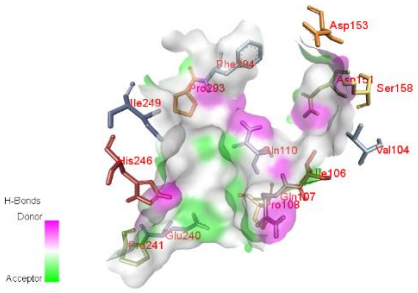



**Figure 1.** Predicted active site of COVID-19 main protease.

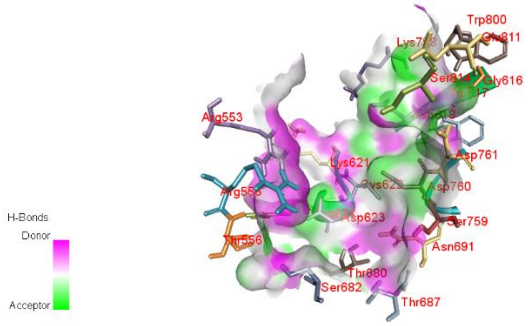



**Figure 2.** Active amino acid residues present in the active site of SARS-CoV-2 RNA-dependent RNA polymerase.

The docking analysis of ivermectin with Mpro revealed the drug's fitting inside the central pocket in association with hydrogen bond with His 246 along with a significant docking affinity of -8.3kcal/mol. High degree binding interactions of ivermectin with RdRp was observed with a promising binding affinity of -9.2 kcal/mol, which is characterized by two hydrogen bonds with Ser 682 and Trp 800, respectively. PASS data also revealed the antiviral activity to some extent. Doramectin was also found to exhibit more affinity for binding towards RdRp. It shows more affinity (-10.0 kcal/mol) compared to Mpro (-8.7 kcal/mol). The affinity of doramectin towards binding with Mpro is still significant to inhibit the protein.

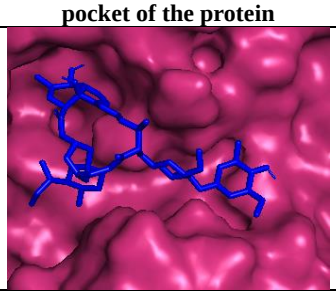
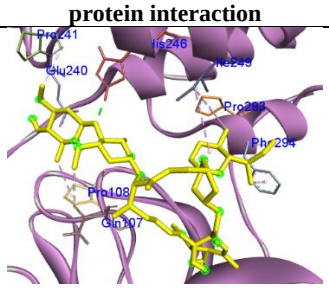
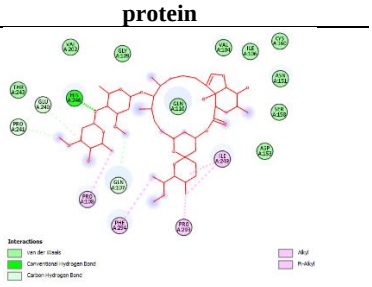
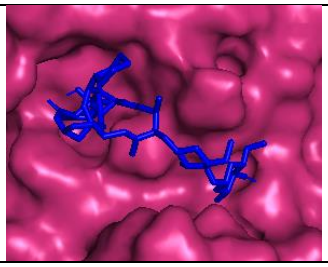
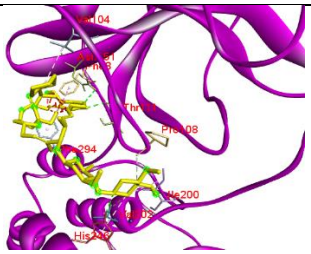
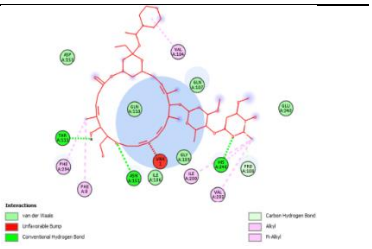
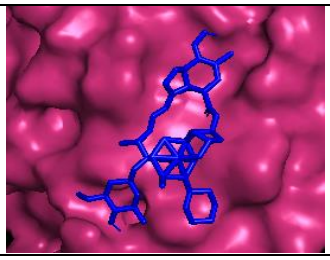
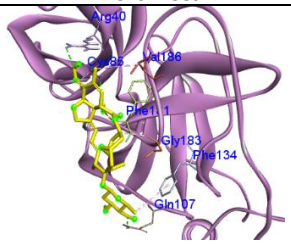
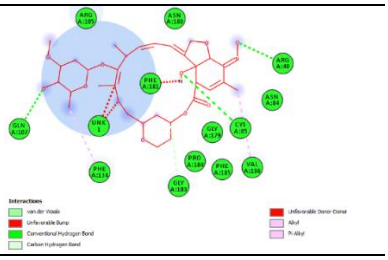
| Best pose of a ligand in the surface pocket of the protein | Amino acid involved in ligand-protein interaction | Interactions of a ligand with the protein |
|---|---|---|
|  |  |  |
| **Ivermectin** | | |
|  |  |  |
| **Doramectin** | | |
|  |  |  |
| **Selamectin** | | |

**Figure 3.** Visualizations of results obtained from docking of compounds with COVID-19 main protease (Mpro).

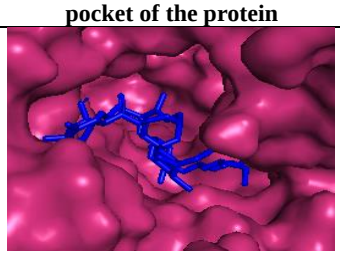
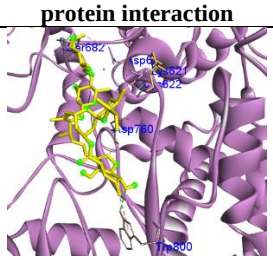
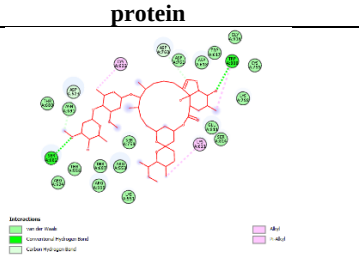
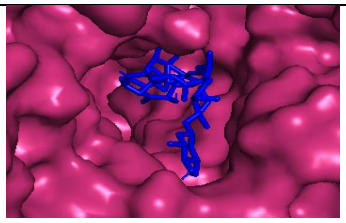
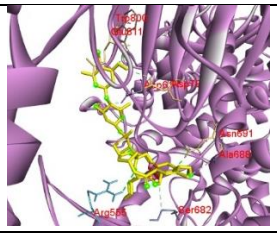
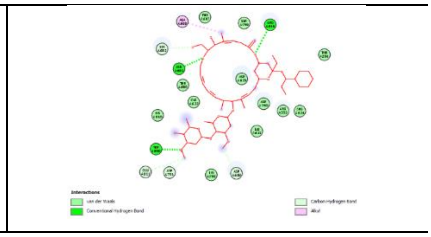
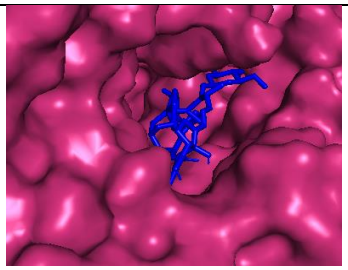
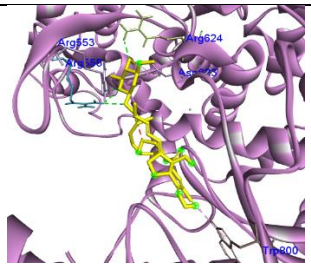
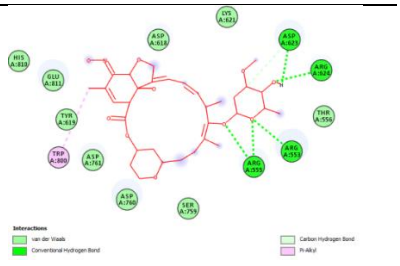
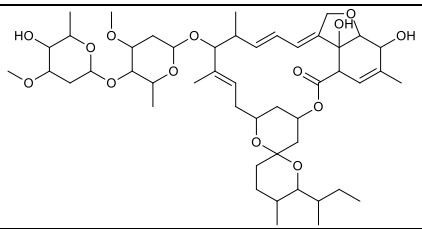
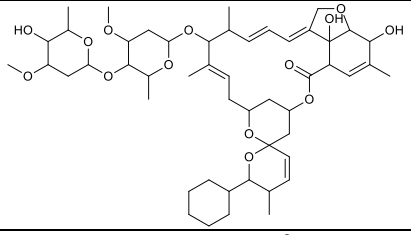
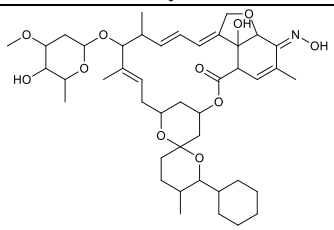
| Best pose of a ligand in the surface pocket of the protein | Amino acid involved in ligand-protein interaction | Interactions of a ligand with the protein |
|---|---|---|
|  |  |  |
| **Ivermectin** | | |
|  |  |  |
| **Doramectin** | | |
|  |  |  |
| **Selamectin** | | |

**Figure 4.** Visualizations of results obtained from docking of compounds with SARS-CoV-2 RNA-dependent RNA polymerase (RdRp).

**Table 1.** Drugs candidates selected for docking with their 2D structures, affinity energies, and activity spectra prediction for substances (PASS) data.

| Compound | 2D Structure | Affinity (kcal/mol) | PASS data | | |
|---|---|---|---|---|---|
| | | | Therapeutic activity | Pa | Pi |
| Ivermectin |  | Mpro: -8.3<br>RdRp: -9.2 | AH<br>AV-R<br>AV-T<br>AV-H | 0,994<br>0,425<br>0,134<br>0,179 | 0,000<br>0,067<br>0,023<br>0,117 |
| Doramectin |  | Mpro: -8.7<br>RdRp: -10 | AH<br>AV-R<br>AV-T<br>AV-H | 0,974<br>0,323<br>0,149<br>0,200 | 0,000<br>0,206<br>0,018<br>0,177 |
| Selamectin |  | Mpro: -9.0<br>RdRp: -10.2 | AH<br>AV-R<br>AV-T<br>AV-H | 0,948<br>0,305<br>0,129<br>0,167 | 0,001<br>0,243<br>0,025<br>0,142 |

Mpro = COVID-19 main protease, RdRp = SARS-CoV-2 RNA-dependent RNA polymerase, AH = Antihelmintic, AV-R = Antiviral (Rhinovirus), AV-T = Antiviral (Trachoma), AV-H = Antiviral (Herpes), Pa = probability of activity, Pi = probability of inactivity.

**Table 2.** Bonding interactions assessment of the best-docked pose of the ligand with COVID-19 main protease.

| Drug | Hydrogen bonds | | Hydrophobic interaction | |
|---|---|---|---|---|
| | Residues | Distance (Å) | Residues | Distance (Å) |
| Ivermectin | His 246 | 1.95 | Thr 243 | 3.21 |
| | | | Val 202 | 3.12 |
| | | | Gly109 | 3.52 |
| | | | Gln 110 | 3.41 |
| | | | Ile 106 | 3.81 |
| Doramectin | Thr 111 | 3.88 | Asp 153 | 3.95 |
| | Asn 151 | 3.01 | Gln 110 | 3.82 |
| | His 246 | 2.88 | Gln 107 | 3.26 |
| | | | Gly 109 | 3.35 |
| Selamectin | Gln 107 | 2.35 | Arg 105 | 3.41 |
| | Cys 85 | 3.45 | Asn 180 | 3.54 |
| | Arg 40 | 2.81 | Asn 84 | 3.98 |
| | | | Gly 179 | 3.45 |
| | | | Phe 185 | 4.25 |

**Table 3.** Bonding interactions assessment of the best-docked pose of the ligand with SARS-CoV-2 RNA-dependent RNA polymerase.

| Drug | Hydrogen bonds | | Hydrophobic interaction | |
|---|---|---|---|---|
| | Residues | Distance | Residues | Distance |
| Ivermectin | Ser 682 | 2.64 | Thr 680 | 2.38 |
| | Trp 800 | 3.04 | Asn 691 | 3.51 |
| | | | Asp 761 | 3.55 |
| | | | Gly 616 | 2.56 |
| | | | Ser 814 | 2.96 |
| | | | Trp 617 | 3.48 |
| | | | Asp 618 | 3.44 |
| | | | Ser 759 | 3.74 |
| Doramectin | Trp 800 | 2.24 | His 810 | 2.47 |
| | Asn 691 | 2.00 | Cys 622 | 2.55 |
| | Arg 555 | 3.04 | Thr 680 | 2.74 |
| | | | Ser 759 | 3.22 |

| | | | | |
|---|---|---|---|---|
| | | | Thr 556 | 3.84 |
| | | | Arg 553 | 2.54 |
| Selamectin | Asp 623 | 2.24 | Asp 618 | 2.14 |
| | Arg 624 | 2.36 | Lys 621 | 2.75 |
| | Arg 553 | 2.37 | Thr 556 | 2.585 |
| | Arg 555 | 2.40 | Asp 761 | 2.35 |
| | Arg 555 | 2.76 | Tyr 619 | 3.25 |
| | | | His 810 | 2.47 |

Doramectin binding with Mpro is attributed by three hydrogen bonds with Thr 111, Asn 151, and His 246, respectively. Similarly, it's binding with RdRp is characterized by 3 hydrogen bonds, specifically with Trp 800, Asn 691, and Arg 555, respectively. The highest binding affinity for binding with RdRp was observed in the case of selamectin, which is -10.2 kcal/mol. This high-affinity binding might have arisen due to the presence of five hydrogen bonds with Asp 623, Arg 624, Arg 553, Arg 555, and Arg 555. PASS data also suggest some extent of anti-rhinoviral activity (Table 1) of selamectin with a pi value of 0,305. Significant binding of selamectin with Mpro was also encountered with an affinity of -9.0 kcal/mol. This binding interaction is characterized by three hydrogen bonds with Gln 107, Cys 85, and Arg 40. Based on the docking assessment results, the anthelmintic drug ivermectin, doramectin, and selamectin were found to exhibit a more binding affinity towards RdRp in comparison with Mpro. Thus, based on this *in silico* assessment, it is quite evident that selected antihelmintic drug candidates exhibit antiviral activity against SARS-CoV-2. Therefore, this study has the potential to invite researchers to explore the *in vivo* activity of the proposed drug candidates.

## 4. Conclusions

Based on the experimental outcomes, it can be concluded that the selected drug candidates possess high binding affinity towards SARS-CoV-2 RNA dependent RNA polymerase. Selected drug candidates, including ivermectin, doramectin, and selamectin, can bind and inhibit COVID-19 main protease and SARS-CoV-2 RNA-dependent RNA polymerase, which is predicted and proved as a result of in silico computational method. These anthelmintic drugs having a promising COVID-19 combating characteristic can be repurposed against COVID-19, a novel enemy of the entire world population.

## Funding

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## Conflicts of Interest

The authors declare no conflict of interest.

## References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; Niu, P.; Zhan, F.; Ma, X.; Wang, D.; Xu, W.; Wu, G.; Gao, G.F.; Tan, W. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England Journal of Medicine* **2020**, *382*, 727–733, https://doi.org/10.1056/NEJMoa2001017.

2. Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K.S.M.; Lau, E.H.Y.; Wong, J.Y.; Xing, X.; Xiang, N.; Wu, Y.; Li, C.; Chen, Q.; Li, D.; Liu, T.; Zhao, J.; Liu, M.; Tu, W.; Chen, C.; Jin, L.; Yang, R.; Wang, Q.; Zhou, S.; Wang, R.; Liu, H.; Luo, Y.; Liu, Y.; Shao, G.; Li, H.; Tao, Z.; Yang, Y.; Deng, Z.; Liu, B.; Ma, Z.; Zhang, Y.; Shi, G.; Lam, T.T.Y.; Wu, J.T.; Gao, G.F.; Cowling, B.J.; Yang, B.; Leung, G.M.; Feng, Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *The New England Journal of Medicine* **2020**, *382*, https://doi.org/10.1056/NEJMoa2001316.
3. Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L.; Chen, H.-D.; Chen, J.; Luo, Y.; Guo, H.; Jiang, R.-D.; Liu, M.-Q.; Chen, Y.; Shen, X.-R.; Wang, X.; Zheng, X.-S.; Zhao, K.; Chen, Q.-J.; Deng, F.; Liu, L.-L.; Yan, B.; Zhan, F.-X.; Wang, Y.-Y.; Xiao, G.-F.; Shi, Z.-L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, *579*, 270–273, https://doi.org/10.1038/s41586-020-2012-7.
4. Weiss, S.R.; Navas-Martin, S. Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. *Microbiology* and *Molecular Biology* Reviews **2005**, *69*, 635–664, https://doi.org/10.1128/MMBR.69.4.635-664.2005.
5. de Wit, E.; van Doremalen, N.; Falzarano, D.; Munster, V.J. SARS and MERS: recent insights into emerging coronaviruses. *Nature Reviews Microbiology* **2016**, *14*, 523–534, https://doi.org/10.1038/nrmicro.2016.81.
6. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; Cheng, Z.; Yu, T.; Xia, J.; Wei, Y.; Wu, W.; Xie, X.; Yin, W.; Li, H.; Liu, M.; Xiao, Y.; Gao, H.; Guo, L.; Xie, J.; Wang, G.; Jiang, R.; Gao, Z.; Jin, Q.; Wang, J.; Cao, B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)* **2020**, *395*, 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
7. Bedford, J.; Enria, D.; Giesecke, J.; Heymann, D.L.; Ihekweazu, C.; Kobinger, G.; Lane, H.C.; Memish, Z.; Oh, M.-D.; Sall, A.A.; Schuchat, A.; Ungchusak, K.; Wieler, L.H. COVID-19: towards controlling of a pandemic. *Lancet (London, England)* **2020**, *395*, 1015–1018, https://doi.org/10.1016/S0140-6736(20)30673-5.
8. Coronavirus Outbreak. Available at: https://www.worldometers.info/coronavirus/. Accessed 5 April 2020.
9. COVID-19 Explainer: Four Stages of Virus Transmission, and What Stage India Currently Finds Itself In (https://weather.com/en-IN/india/coronavirus/news/2020-04-09-four-stages-of-virus-transmission-stage-india-currently-finds).
10. Rodríguez-Morales, A.J.; MacGregor, K.; Kanagarajah, S.; Patel, D.; Schlagenhauf, P. Going global - Travel and the 2019 novel coronavirus. *Travel Medicine and Infectious Disease* **2020**, *33*, https://dx.doi.org/10.1016%2Fj.tmaid.2020.101578.
11. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.-H.; Nitsche, A.; Müller, M.A.; Drosten, C.; Pöhlmann, S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **2020**, *181*, 271-280.e8, https://doi.org/10.1016/j.cell.2020.02.052.
12. Kai, H.; Kai, M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. *Hypertension Research* **2020**, *43*, 648-654, https://doi.org/10.1038/s41440-020-0455-8.
13. Magrone, T.; Magrone, M.; Jirillo, E. Focus on Receptors for Coronaviruses with Special Reference to Angiotensin-converting Enzyme 2 as a Potential Drug Target - A Perspective. *Endocrine*, Metabolic and *Immune Disorders - Drug Targets* **2020**, *20*, https://doi.org/10.2174/1871530320666200427112902.
14. Zhang, L.; Lin, D.; Sun, X.; Curth, U.; Drosten, C.; Sauerhering, L.; Becker, S.; Rox, K.; Hilgenfeld, R. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors. *Science (80-. ).* **2020**, *368*, 409–412, https://doi.org/10.1126/science.abb3405.
15. Joshi, R.S.; Jagdale, S.S.; Bansode, S.B.; Shankar, S.S.; Tellis, M.B.; Pandya, V.K.; Chugh, A.; Giri, A.P.; Kulkarni, M.J. Discovery of potential multi-target-directed ligands by targeting host-specific SARS-CoV-2 structurally conserved main protease. *Journal* of *Biomolecular Structure* and *Dynamics* **2020**, 1–16, https://doi.org/10.1080/07391102.2020.1760137.
16. Gao, Y.; Yan, L.; Huang, Y.; Liu, F.; Zhao, Y.; Cao, L.; Wang, T.; Sun, Q.; Ming, Z.; Zhang, L.; Ge, J.; Zheng, L.; Zhang, Y.; Wang, H.; Zhu, Y.; Zhu, C.; Hu, T.; Hua, T.; Zhang, B.; Yang, X.; Li, J.; Yang, H.; Liu, Z.; Xu, W.; Guddat, L.W.; Wang, Q.; Lou, Z.; Rao, Z. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science (80-.)* **2020**, *368*, 779–782, https://doi.org/10.1126/science.abb7498.
17. Narkhede, R.R.; Cheke, R.S.; Ambhore, J.P.; Shinde, S.D. The Molecular Docking Study of Potential Drug Candidates Showing Anti-COVID-19 Activity by Exploring of Therapeutic Targets of SARS-CoV-2. *Eurasian Journal of Medicine and Oncology* **2020**, *4*, 185-195, https://doi.org/10.14744/ejmo.2020.31503.
18. Narkhede, R.R.; Pise, A. V; Cheke, R.S.; Shinde, S.D. Recognition of Natural Products as Potential Inhibitors of COVID-19 Main Protease (Mpro): In-Silico Evidences. *Natural Products and Bioprospecting* **2020**, *10*, 297-306, https://doi.org/10.1007/s13659-020-00253-1.
19. Bangladesh Medical Team Claims Ivermectin With Doxycycline Clears COVID-19. Available at https://worldhealth.net/news/bangladesh-medical-team-claims-ivermectin-doxycycline-clears-covid-19/ Accesed on: 28 May, 2020.

20. Sodhi, M.; Etminan, M. Therapeutic Potential for Tetracyclines in the Treatment of COVID-19. *Pharmacotherapy* **2020**, *40*, 487–488, https://doi.org/10.1002/phar.2395.
21. Caly, L.; Druce, J.D.; Catton, M.G.; Jans, D.A.; Wagstaff, K.M. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Research* **2020**, *178*, https://doi.org/10.1016/j.antiviral.2020.104787.
22. Bray, M.; Rayner, C.; Noël, F.; Jans, D.; Wagstaff, K. Ivermectin and COVID-19: A report in Antiviral Research, widespread interest, an FDA warning, two letters to the editor and the authors' responses. *Antiviral Research* **2020**, *178*, https://doi.org/10.1016/j.antiviral.2020.104805.
23. Momekov, G.; Momekova, D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: antiviral levels are not likely attainable with known dosing regimens. *medRxiv* **2020**, https://doi.org/10.1101/2020.04.11.20061804.
24. Cousins, K. Computer Review of ChemDraw Ultra 12.0. *Journal of the American Chemical Society* **2011**, *133*, https://doi.org/10.1021/ja204075s.
25. Pedretti, A.; Villa, L.; Vistoli, G. VEGA--an open platform to develop chemo-bio-informatics applications, using plug-in architecture and script programming. *Journal* of *computer-aided molecular design* **2004**, *18*, 167–173, https://doi.org/10.1023/b:jcam.0000035186.90683.f2.
26. Morris, G.M.; Huey, R.; Lindstrom, W.; Sanner, M.F.; Belew, R.K.; Goodsell, D.S.; Olson, A.J. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal* of *Computational Chemistry* **2009**, *30*, 2785–2791, https://doi.org/10.1002/jcc.21256.
27. Jin, Z.; Du, X.; Xu, Y.; Deng, Y.; Liu, M.; Zhao, Y.; Zhang, B.; Li, X.; Zhang, L.; Peng, C.; Duan, Y.; Yu, J.; Wang, L.; Yang, K.; Liu, F.; Jiang, R.; Yang, X.; You, T.; Liu, X.; Yang, X.; Bai, F.; Liu, H.; Liu, X.; Guddat, L.W.; Xu, W.; Xiao, G.; Qin, C.; Shi, Z.; Jiang, H.; Rao, Z.; Yang, H. Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature* **2020**, *582*, 289-293, https://doi.org/10.1038/s41586-020-2223-y.
28. Trott, O.; Olson, A.J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal* of *Computational Chemistry* **2010**, *31*, 455–461, https://doi.org/10.1002/jcc.21334.
29. Yuan, S.; Chan, H.C.S.; Hu, Z. Using PyMOL as a platform for computational drug design. *WIREs Computational molecular science* **2017**, *7*, https://doi.org/10.1002/wcms.1298.
30. Lagunin, A.; Stepanchikova, A.; Filimonov, D.; Poroikov, V. PASS: prediction of activity spectra for biologically active substances. *Bioinformatics* **2000**, *16*, 747–748, https://doi.org/10.1093/bioinformatics/16.8.747.