Rapid investigation into the identification of the potential inhibitors of SARS CoV-2 using virtual screening, molecular dynamic simulation and ADMET analysis

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ABSTRACT

The COVID-19 epidemic has been causing concern for the majority of the world for the past two years. More than 5.6 million people have died globally, according to current estimates from the WHO. The virus is still evolving globally, necessitating both attention and the development of various possible treatments, involving the identification of particular anti-viral medications. The use of SARS-membrane-bound CoV-2's spike protein to detect human angiotensin-converting enzyme 2 has been demonstrated in several investigations (ACE2). Therefore, blocking spike-ACE2 interactions could be a promising and effective method of treating COVID-19 because it can prevent the virus from attaching to and entering into the host cell. Using an in silico method, this research seeks to identify novel medications. Both licenced medications and compounds that had already undergone in vivo testing were subjected to molecular docking. The best ligands were then identified by performing analysis of the specified ligands by molecular dynamics simulations.

KEYWORDS – SARS-CoV, COVID-19, OPLS, docking study, ADMET

INTRODUCTION

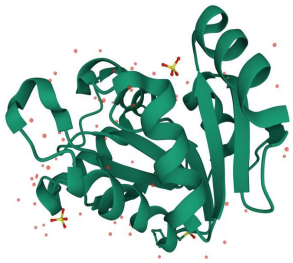
The effects of COVID-19 are felt widely by individuals, groups, and entire cultures. Immuno-compromised people are more susceptible to COVID-19 than other populations.[1] The virus belongs to the Coronoviridae family, which also includes other viruses that may infect humans, such as SARS-CoV, which resulted into pandemic in 2002–2004.[2] There are over 19 million COVID-19 infections worldwide. The SARS Coronavirus 2 (SARS CoV-2) is the virus that resulted into outbreak.[3-4] A high-risk COVID-19 case occurs when there are underlying infections such as heart failure, diabetes, coronary artery disease, chronic obstructive

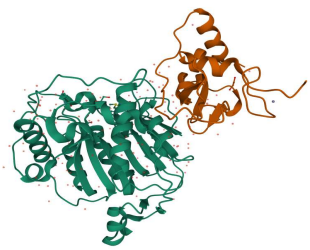
pulmonary disease, cardiomyopathy as well as weak immune conditions [5]. The significant rise of COVID-19 cases across a number of countries has been attributed to the introduction of new SARS-CoV-2 variants, particularly VOCs like Beta, Alpha and Delta [6-7]. Since the COVID-19 epidemic began, other SARS-CoV-2 variants have been discovered. These variations have resulted in increased mortality rates in a number of nations.[8] China, the first country to be affected by a new coronavirus, has reacted favourably by taking a number of preventive measures. Some of these strategies include lockdowns, quarantines, isolations, hygienic practises, routine hand washing, etc. that seem to reduce the broad and community-based transmission.[9-11]

MATERIAL AND METHODS

Preparation of protein structure and receptor grid genenration for virtual screening

The three protein structures namely PDB ID: **6VXS**, **6WPS, 6W61** were retrieved from Protein Data Bank (PDB) and were processed by using the Protein Preparation Wizard. It comprises mainly optimization of hydrogen bond, assignment of bond order and constraint minimization to remove steric clashes The missing side-chain information of the residues was modeled with the help of Schrodinger Prime. The process of energy minimization was performed by applying the standard OPLS. There is OPLS-AA (all-atom) includes every atom explicitly, OPLS-UA (united atom) which includes hydrogen atoms next to carbon implicitly in the carbon parameters, and can be used to save simulation time, later publication include parameters for other specific functional groups and types of molecules such as carbohydrates. OPLS simulations force field in an aqueous solution typically use the TIP4P OR TIP3P model. OPLS-2001 and OPLS- 20059 are the latest algorithms of OPLS force field.





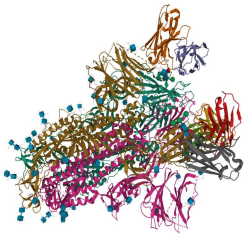


Figure 1 shows PDB ID: 6VXS **Figure 2 shows PDB ID: 6WPS** **Figure 3 shows PDB ID: 6W61**

Structure based pharmacophoric model generation.

The structure-based pharmacophore model generation mainly utilizes the spatial information of the target protein for the topological description of ligand-receptor interaction. The energetically optimized structure based pharmacophore uses combined feature of receptor structure and ligands. Therefore, receptor grid was generated for 6VXS, 6WPS and 6W61 complex in glide module and subsequently these proteins were re-docked using Glide XP docking module to obtain the interaction and energetic score profile.

All the three receptors were flexibly docked and XP descriptor information was used to obtain the detailed energetic information of the complex in order to get the important pharmacophoric features. The pharmacophore model of docked complex with these receptors were generated by using E- pharmacophore module in Maestro Schrodinger 9.2 eventually considered maximum seven feature namely hydrogen bond acceptor (A), hydrogen bond donors (D), hydrophobes (H) and aromatic rings (R).

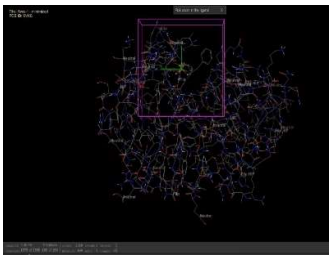


Figure 4 shows grid PDB ID: 6VXS

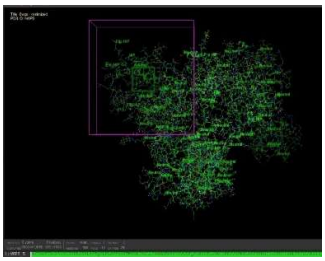


Figure 5 shows grid PDB ID: 6WPS

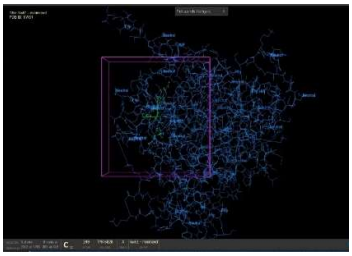


Figure 6 shows grid PDB ID: 6W61

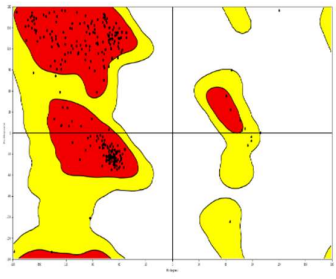


Figure 7 shows ramachandran plot PDB ID : 6VXS

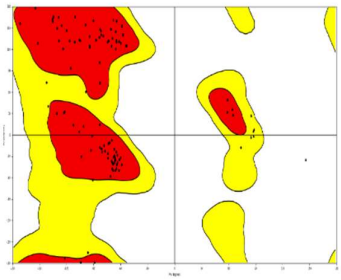


Figure 8 shows ramachandran plot PDB ID: 6WPS

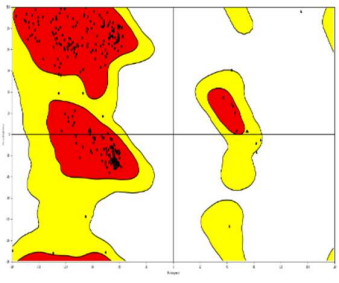


Figure 9 shows ramachandran plot PDB ID : 6W61

Molecule Library Generation

The entire library of approximate 15,685 compounds and their derivatives were retrieved from various databases such as Anticancer Library . All the designated compounds were prepared and optimized with energy minimization, and their 3D structure were generated using Maestro LigPrep. The final phase database library was created for the entire natural compound library using PHASE module Schrodinger 9.2, which generated at low energy 3D structure of library and subjected for screening.

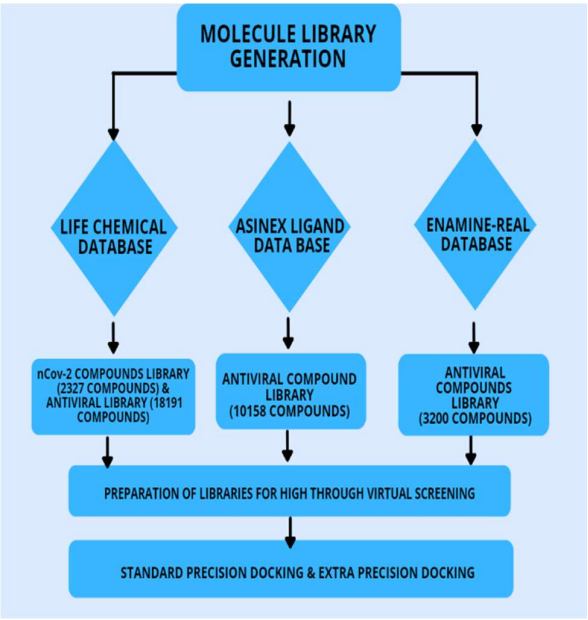


Figure 10. Work flow of molecule library generation

Molecular Docking

All the screened ligands were identified for molecular docking study against recptors to screen out the best fit compounds in the pocket. The previously generated receptor grid was used for molecular docking of the screened ligands. The molecular docking study was performed consecutively in three steps- High through put screening(HTS), Standard precision (SP) algorithm and Extra precision (XP) algorithm which gives more rigorous penalties to the ligand poses for docking pocedure using Maestro Schrodinger 9.2

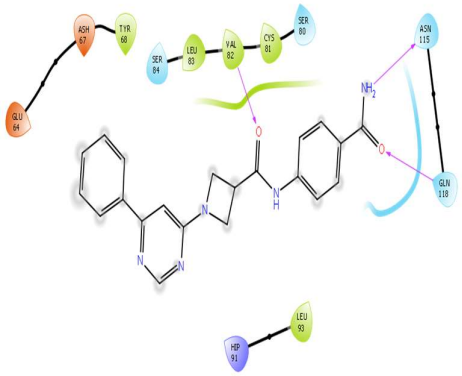


Figure 11- Ligand Interaction of Ligand (F6495-3952)

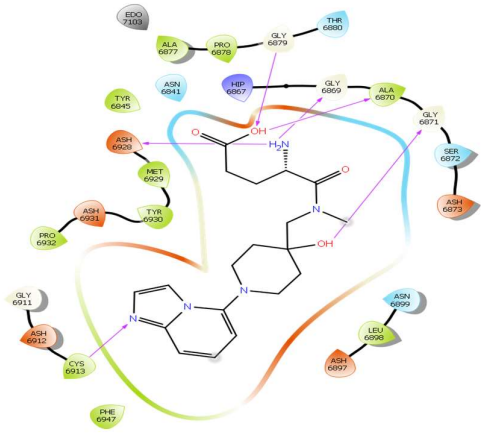


Figure 11- Ligand Interaction of Ligand F6458-5529

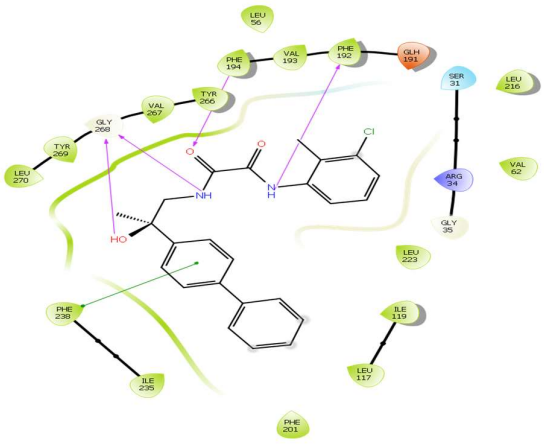


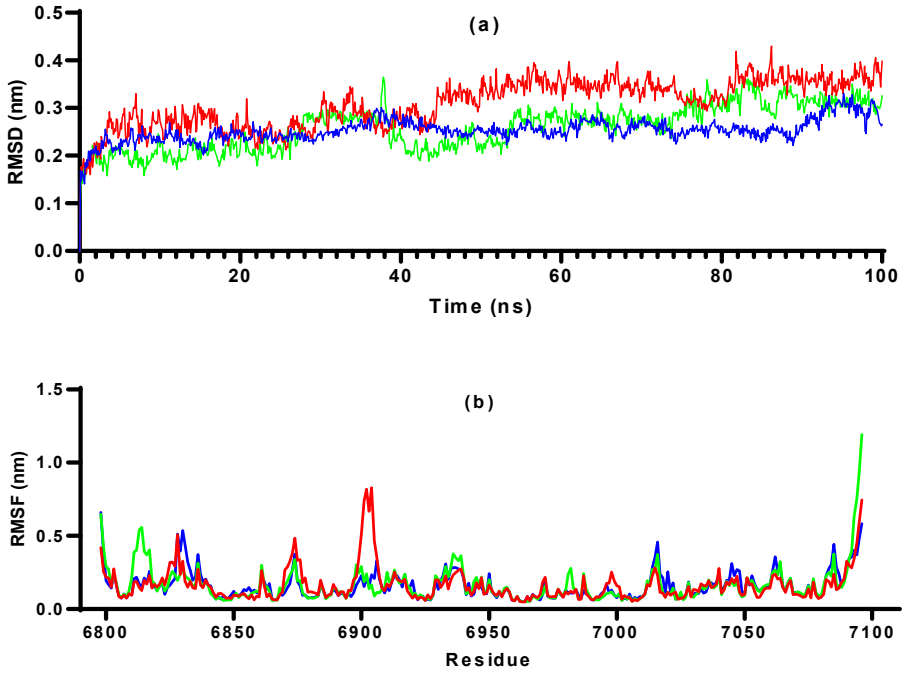
Figure 11 -Ligand Interaction of Ligand (F5857-2926)

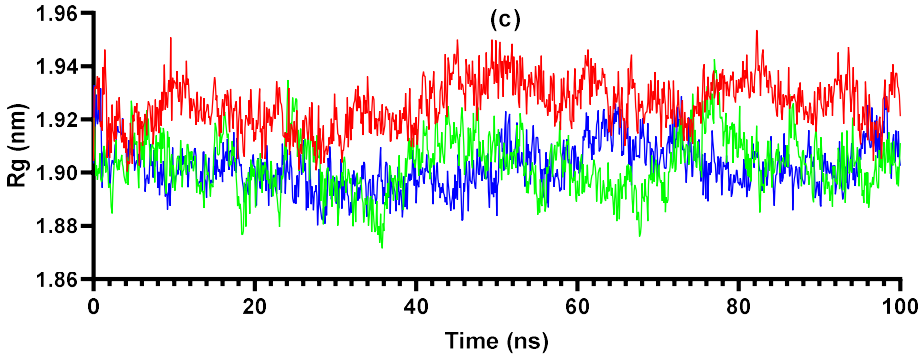
Molecular dynamics simulation

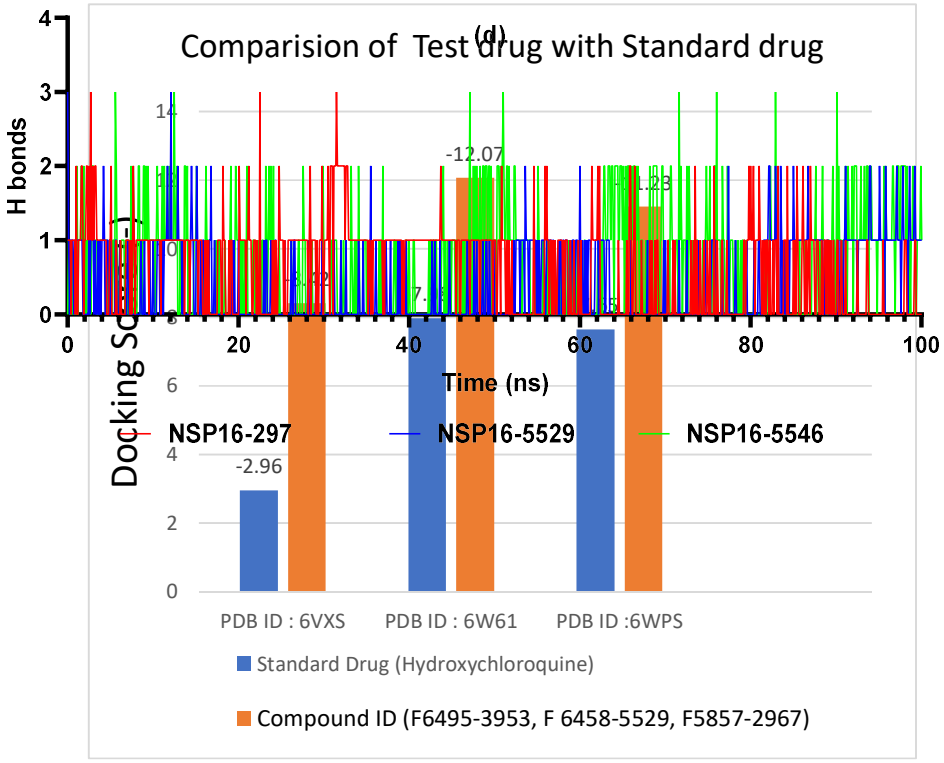
The molecular dynamics simulation was performed with the help of Gromacs 2019.2 version (GROningen Machine for Chemical Simulations) to find out the protein-ligand complex's stability via WebGRO for macromolecular simulations. Inspite of the findings that crystallography show clearly how essential a role protein flexibility plays in ligand binding, the cost and time-consuming nature of producing them has prompted many to turn to the computational techniques that were developed in the 1970s. [12] The molecular framework is one of the most employed computer based model utilize information from nuclear magnetic resonance (NMR), crystallography, or homology mapping.[13]. Simple virtual springs are utilized to recreate chemical bonds and atomic angles, and a sinusoidal function is implemented to simulate dihedral angles (rotations about bonds), which substantially resemble the energy discrepancies between eclipsed and staggered conformations. Van der Waals interactions, which are depicted using the Lennard-Jones 6- 12 potential, emerge to non-bonded forces. [14]

S. No.	Parameters (Energy, kJ/mol)	Enzyme-ligand complexes		
		NSP16-297	NSP16-5529	NSP16-5546
1	Van der Waals	-.927±20.951	-115.040±15.113	-114.606±15.471
2	Electrostatic	-14.847±9.979	-16.206±17.914	-16.509±8.506
3	Polar solvation	71.704±13.302	86.193±27.027	55.760±13.077
4	SASA	-16.925±1.499	-13.467±1.921	-11.678±1.413
5	Binding free	-129.994±20.452	-58.521±11.022	-87.033±12.435

Table 1. shows the MM-PBSA calculations of binding free energy of selected complexes between 80 ns and 100 ns







Graph 1 - Comparision of the test drug with standard drug

S. No.	Compound Name	Lipophilicity (Log Po/w)	Water Solubility (Class)	Pharmacokinetic (GI absorption)	% Oral Absorption	Carcinogenicity	Acute oral toxicity (c)
1	F6495-3952	2.39	Soluble	High	100	Not required	III
2	F6458-5529	2.46	Soluble	High	88.50	Not required	III
3	F5857-2967	3.07	Moderately Soluble	High	93.42	Not required	III

Table 2. Physiochemical Properties of the screened three compounds

Result

We have been isolated top 3 docking compounds for analysing their docking pose, interaction with particular amino acid residue, surface interaction and the 3-Dimensional interaction. It helps to find out the accurate binding pose between the receptor and compounds

CONCLUSION

This investigation has used the ADP ribose phosphate of NSP3 from SARS CoV-2 (PDB ID: 6VXS), methyl transferase-stimulatory from SARS CoV-2 (PDB ID: 6W61), Spike glycoprotein (PDB ID: 6WPS) are essential for the viability of SARS CoV-2. The study examined 33,876 identical compounds. from Life chemical, Enamine-real database and Asinex database to screen out the potential drug molecule through computational drug designing techniques.

According to the molecular docking data, SARS CoV-2's target protein and the virus have a high binding affinity. The ligands that have been discovered all have antiviral properties. On the basis of Lipinski's rule of five, involving water solubility, lipophilicity, pharmacokinetics, and pharmacodynamic profile, in-silico virtual screening methods aid in the design of the potent drug candidate. For each receptor, the top 3 molecules all exhibit exceptional docking scores and binding energies. Three chemical compounds have been identified through docking and MDSs research that may be potential therapeutic molecules against the methyl-transferase-stimulatory from SARS CoV-2 (PDB ID: 6W61). For PDB ID: 6W61 compounds 297, 5529 and 5546 having an antiviral activity. Optimistic parameter values for intermolecular hydrogen bonding, RMSD, RMSF, RoG, binding free energy for 100 ns are present in all three ligand-protein complexes. Therefore it might be useful to investigate these substances (F6495-3952, F6458-5529, and) further more to validate the *in vitro* findings against SARS CoV-2.

REFRENCES

1. C. Titany, G. Kemesha, H. Patricia, H. Cashea, The impact of COVID-19 on HIV treatment and research: a call to action, Int. J. Environ. Res. Publ. Health 17 (2020) 45–48.

2. J.D. Cherry, P.Krogstad, SARS: the first pandemic of the 21st century,Pediatr.Res. 56 (1) (2004)1–5.

3. Y. Jin, H. Yang, W. Ji, W. Wu, S. Chen, W. Zhang, G. Duan, Virology, epidemiology, pathogenesis, and control of COVID-19, Viruses 12 (2020) 372.

4. M. Nicola, N. O'Neill, C. Sohrabi, M. Khan, M. Agha, R. Agha, Evidence based management guideline for the COVID-19 pandemic - review article, Int. J. Surg. 77 (2020) 206–216, https://doi.org/10.1016/j.ijsu.2020.04.001.

5. B. Joob, V. Wiwanitkit, SARS-CoV-2 and HIV, J. Infect. 66 (2020) 439–446.

6. A.M. Tareq, T. Bin Emran, K. Dhama, M. Dhawan, T.E. Tallei, Impact of SARS-CoV 2 delta variant (B.1.617.2) in surging second wave of COVID-19 and efficacy of vaccines in tackling the ongoing pandemic, Hum. Vaccines Immunother. 17 (2021) 4126–4127, https://doi.org/10.1080/21645515.2021.1963601.

7. A. Fontanet, B. Autran, B. Lina, M.P. Kieny, S.S.A. Karim, D. Sridhar, SARS-CoV-2 variants and ending the COVID-19 pandemic, Lancet 397 (2021) 952–954, https:// doi.org/10.1016/S0140-6736(21)00370-6.

8. W.T. Harvey, A.M. Carabelli, B. Jackson, R.K. Gupta, E.C. Thomson, E.M. Harrison, C. Ludden, R. Reeve, A. Rambaut, S.J. Peacock, D.L. Robertson, SARS-CoV-2 variants, spike mutations and immune escape, Nat. Rev. Microbiol. 19 (2021) 409–424, https://doi.org/10.1038/s41579-021-00573-0.

9. N. Usman, M.A. Mamun, I. Ullah, COVID-19 infection risk in pakistani health-care workers: the cost-effective safety measures for developing countries, Soc. Health Behav. 3 (2020) 75, https://doi.org/10.4103/SHB.SHB_26_20.

10.D.D. Dsouza, S. Quadros, Z.J. Hyderabadwala, M.A. Mamun, Aggregated COVID-19 suicide incidences in India: fear of COVID-19 infection is the prominent causative factor, Psychiatr. Res. 290 (2020) 113145, https://doi.org/10.1016/j. psychres.2020.113145

11. M. Jakovljevic, S. Bjedov, N. Jaksic, I. Jakovljevic, COVID-19 pandemia and public and global mental health from the perspective of global health securit, Psychiatr. Danub. 32 (2020) 6–14, https://doi.org/10.24869/psyd.2020.6.

12. McCammon JA, Gelin BR, Karplus M: Dynamics of folded proteins. Nature 1977, 267:585-590.

13. Cornell WD, Cieplak P, Bayly CI, Gould IR, Merz KM, Ferguson DM, Spellmeyer DC, Fox T, Caldwell JW, Kollman PA: A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. J Am Chem Soc 1995, 117:5179-5197.

14. Lennard-Jones JE: On the determination of molecular fields. II. From the equation of state of a gas. Proc R Soc Lond A 1924, 106:463-477.