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Fast Tracking the Discovery of SARS-CoV-2 Inhibitors through Virtual Screening, Molecular Dynamic Simulation, and ADMET Analysis

Shaikh AA[1]*, Pawar JB[2] and Anbhule SJ[3]

[1]Department of Pharmacy, Savitribai Phule Pune University, India

[2]Department of Microbiology, Savitribai Phule Pune University, India

[3]Department of Medical Chemistry, Savitribai Phule Pune University, India

***Corresponding author:** Afroj A Shaikh, Department of Pharmacy, Savitribai Phule Pune University, Kashti, Shrigonda 413701, India, Email: afrojs952@gmail.com

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Abstract

For the past two years, the COVID-19 pandemic has worried the majority of the world. The WHO's most recent figures indicate that more than 5.6 million people have passed away globally. A variety of potential treatments, including the identification of specific anti-viral drugs, must be developed because the virus is still evolving on a worldwide scale. Numerous studies have shown the ability of the CoV-2 spike protein to identify human angiotensin-converting enzyme 2. (ACE2). In light of the fact that it can stop COVID-19 from adhering to and entering the host cell, inhibiting spike-ACE2 interactions may be a potential and effective means of treating the virus. This study aims to find new medicines using an in silico approach. Molecular docking was used to substances that had already undergone in vivo testing as well as licenced pharmaceuticals. The best ligands were then found by running molecular dynamics simulations to analyse the given ligands..

Keywords: SARS-CoV; COVID-19; OPLS; Docking Study; ADMET

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; PDB: Protein Data Bank; HTS: High Throughput Screening; SP: Standard Precision; XP: Extra Precision.

Introduction

Individuals, groups, and entire cultures are all affected negatively by COVID-19. Compared to other groups, immuno-compromised people are more vulnerable to COVID-19 [1]. The virus is a member of the Coronoviridae family, which also includes other viruses that can infect people, such as the SARS-CoV virus that caused the pandemic in 2002–2004. Infections with COVID-19 total more than 19 million across the globe [2]. The virus responsible for the outbreak is the SARS Coronavirus 2 (SARS CoV-2) [3-4]. When disorders with weakened immune systems, such as heart failure, diabetes, coronary artery disease, chronic obstructive pulmonary disease (COPD), cardiomyopathy, and other underlying infections are present, the COVID-19 case is considered to be high-risk [5]. New SARS-CoV-2 variations, especially VOCs like Beta, Alpha, and Delta, have been blamed for the sharp increase in COVID-19 cases in a number of nations [6-7]. Other SARS-CoV-2 variants have been found since the COVID-19 epidemic started. In a handful of countries, these

variances have led to rising death rates [8]. As the first nation to experience a novel coronavirus, China has responded well by implementing a number of preventative measures. Among these tactics are lockdowns, quarantines, isolations, hygienic practises, regular hand washing, etc. that appear to lessen the broad. Some of these tactics, which appear to lessen the widespread and community-based transmission, include lockdowns, quarantines, isolations, sanitary practises, routine hand washing, etc [9-11].

Material and Methods

Preparation of Protein Structure and Receptor Grid Generation for Virtual Screening

The Protein Preparation Wizard was used to process the three protein structures, which were obtained from the Protein Data Bank (PDB) under the PDB IDs 6VXS, 6WPS, and 6W61. To avoid steric conflicts, it primarily entails hydrogen bond optimization, bond order assignment, and constraint minimization. With the use of Schrodinger Prime, the residues' missing side-chain information was modeled. By using the conventional OPLS, the energy minimization method was carried out. There are two types of OPLS: OPLS-AA (all-atom), which explicitly includes every atom, and OPLS-UA (united atom), which implicitly includes hydrogen atoms next to carbon in the carbon parameters. These can be used to speed up simulations. Later publications will also include parameters for other specific functional groups and types of molecules, like carbohydrates. In most cases, the TIP4P OR TIP3P model is used in OPLS simulations of the force field in an aqueous solution. The most recent OPLS force field algorithms are OPLS-2001 and OPLS-20059 (Figure 1).

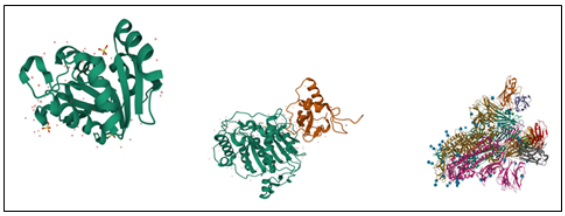

Figure 1: shows (a) PDB ID: 6VXS (b) PDB ID: 6WPS (c) PDB ID: 6W61.

Structure Based Pharmacophoric Model Generation

The target protein's spatial information is mostly used by the structure-based pharmacophore model creation to describe the topology of ligand-receptor interactions. The energetically optimised structure-based pharmacophore makes use of both ligands and receptor structure. In order to obtain the interaction and energetic score profile, the receptor grid for the 6VXS, 6WPS, and 6W61 complex was created in the glide module. Then, these proteins were re-docked using the Glide XP docking module.

In order to identify the key pharmacophoric properties of the complex, all three receptors were flexible docked, and XP descriptor information was used to acquire the complex's full energetic information. Utilizing Maestro Schrodinger 9.2's E-pharmacophore module, the pharmacophore model of the docked complex containing these receptors eventually took into account a maximum of seven features, including hydrogen bond acceptors (A), donors (D), hydrophobes (H), and aromatic rings (R) (Figure 2).

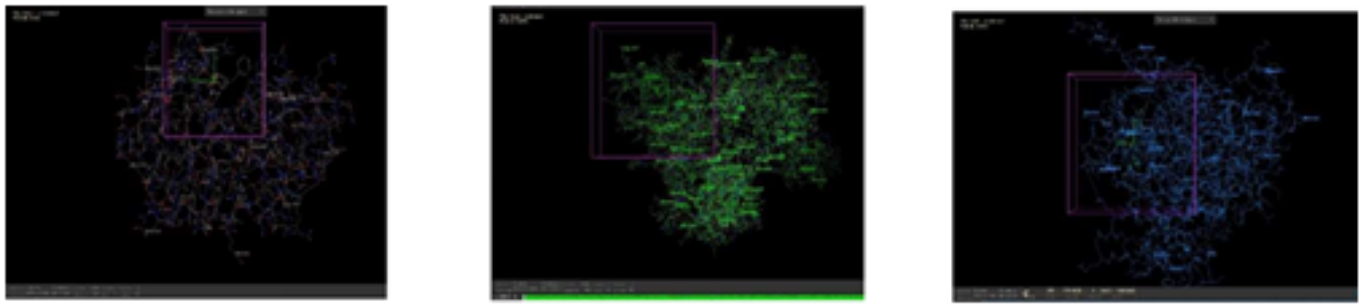

Figure 2: shows grid (a) PDB ID: 6VXS; (b) PDB ID: 6WPS; (c) PDB ID: 6W61.

Molecule Library Generation

From several databases, including the Anticancer Library, the complete library of roughly 15,685 chemicals and their derivatives was gathered. Using Maestro LigPrep, the 3D structures of all the specified compounds were created and prepared while minimising energy consumption. Using the PHASE module Schrodinger 9.2, which constructed the library's 3D structure at low energy and submitted it to screening, the final phase database library was produced for the whole collection of natural compounds (Figure 3).

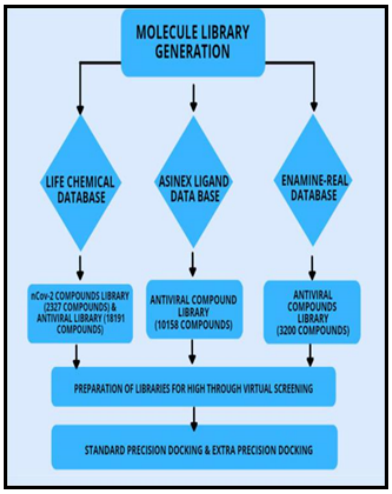

Figure 3: Work flow of molecule library generation.

Molecular Docking

For the purpose of identifying the molecules that would fit the pocket the best, all the screened ligands were identified for molecular docking analysis against receptors. The screened ligands were molecularly docked onto the previously created receptor grid. The molecular docking investigation was carried out sequentially in three steps utilising Maestro Schrodinger 9.2 and the High Throughput Screening (HTS), Standard Precision (SP), and Extra Precision (XP) algorithms, which impose increasingly stringent penalties on the ligand poses for docking procedure.9.2 (Figure 4).

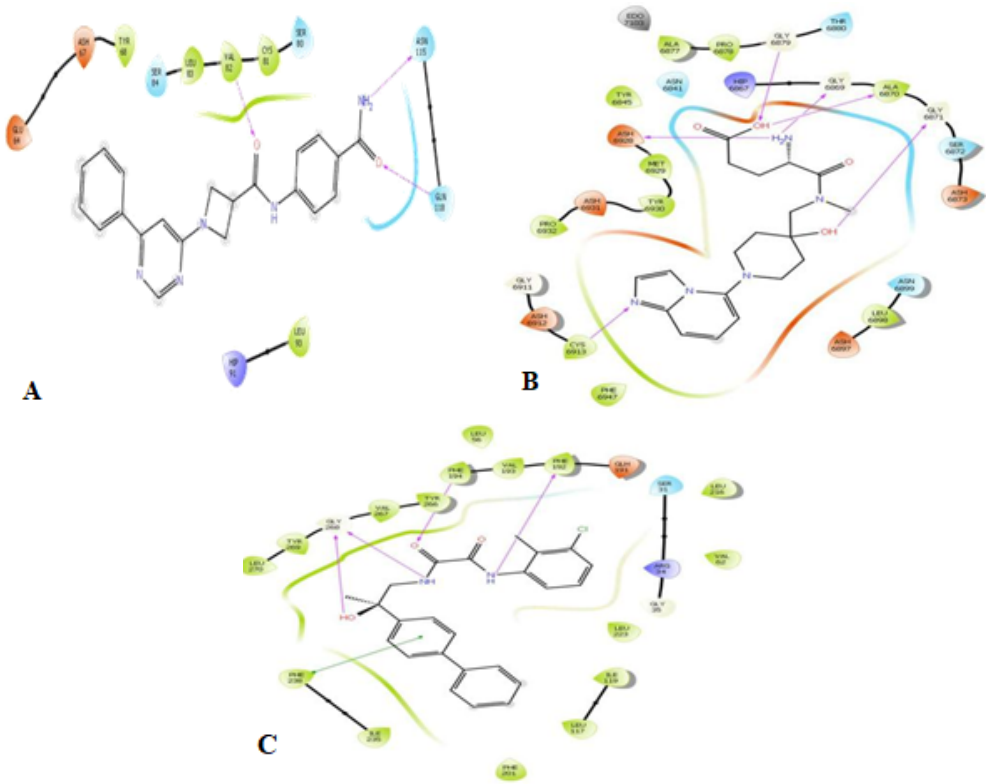

Figure 4: (A) Ligand Interaction of Ligand (F6495-3952); (B) Ligand Interaction of Ligand (F6495-5529); (C) Ligand Interaction of Ligand (F5857-2926).

Molecular Dynamics Simulation

The Gromacs 2019.2 version (GROningen Machine for Chemical Simulations) was used to run a molecular dynamics simulation in order to determine the stability of the protein-ligand combination using WebGRO. Despite the fact that crystallography has demonstrated the crucial function that protein flexibility plays in ligand binding, many researchers have instead turned to the computational methods that were created in the 1970s due to the expense and labor-intensive nature of their production [12]. One of the most frequently used computer-based models uses data from nuclear magnetic resonance (NMR), crystallography, or homology mapping. This model is called the molecular framework [13]. Simple virtual springs are used to model atomic and chemical angles, and a sinusoidal function is used to represent dihedral angles (rotations about bonds), which closely resemble the energy of rotations (Tables 1 & 2), (Figure 5) [14].

Sr. No.	Parameters (Energy, kJ/mol)	Enzyme-ligand complexes		
		NSP16-297	NSP16-5529	NSP16-5546
1	Van der Waals	-0.927 ± 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.

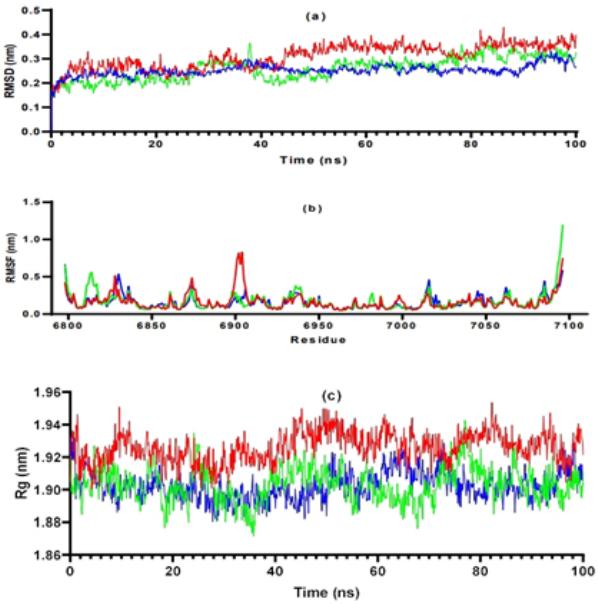

Figure 5: Graphical Representation.

Sr. No.	Compound Name	Lipid Solubility	Water Solubility (Class)	Pharmacokinetics (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	88.5	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

The top three docking compounds have been narrowed down for analysis of their docking pose, interaction with a specific amino acid residue, surface interaction, and three-dimensional interaction. It aids in determining the precise binding position of the chemicals on the receptor.

Conclusion

In above investigation, the researchers used computational drug designing tools to screen potential therapeutic molecules from chemical databases for their efficacy against SARS CoV-2. They focused on curial components of the viruses, including ADP ribose phosphate of NSP3, methyl transferase-stimulatory from SARSCoV-2 and spike glycoprotein. Molecular docking data showed a strong affinity between the target proteins and the viruses. The ligands identified displayed antiviral characteristics and met Lipinski's rule of five. The top 3 compounds exhibited remarkable docking scores and binding energies. Notably, three chemical compounds (297, 5529 and 5546) neutralized the methyl-transferase-stimulatory protein (PDB ID: 6W61) through docking and MDSs Study.

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Conflict of Interest

No Conflict of interest.

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