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Protein-Ligand In- Silico Molecular Docking Model for Discovering Potential Drugs of COVID-19

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Abstract—

The novel human coronavirus is known as SARS-CoV-2, first noticed in late 2019 in Wuhan, China causing a respiratory disease known as COVID-19. This disease has extended rapidly around the world, leading to neuroma deaths and economic losses across many countries. There is currently no approved therapeutics, and effective treatment alternatives remain extremely limited; treating is a pressing need. This work aims to find a potential drug candidate by finding the effective binding between a small molecule (ligand) and a protein by applying protein-ligand docking for target 6YNQ Main protease (Mpro) protein using the AutoDock Vina technique. Several compounds have been identified from the in-silico docking model that could prove effective inhibitors for SARS-CoV-2. Among those compounds and related drugs, 5 best compounds were selected, which had a better score and lower root-mean-square deviation as compared to the reference molecule as: 1.067 Å, 1.78 Å, 1.648 Å, 1.533 Å, and0.027 Å. Results revealed that the identified compounds and drugs (Nintedanib, Nifedipine, NNRTI, and Bordetella pertussis toxoid antigen) are recommended for therapeutic development against the virus as these novel molecules may be utilized to advance innovation and development of antiviral compounds among Coronavirus.

Keywords: SARS-CoV-2 ; *COVID-19*; *protein-ligand docking*; *AutoDock Vina*; *Mpro.*

I. INTRODUCTION

COVID-19 is an extremely contagious disease associated with a high death rate. As of 25 November 2020, **59,204,902** confirmed instances of COVID-19 were reported in China and 216 other countries, including **1,397,139** deaths [1], which poses a grave threat to global public health. In December 2019, officials in Wuhan City, China first reported the human instances of COVID-19, the disease duo to the novel coronavirus causing COVID-19, later called SARS-CoV-2 were first by Retrospect [1].

Asking for the timely advancement of a particular therapeutics and prophylactics anti-coronavirus treatment for the diagnosis and avoidance of COVID-19, it brought about by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-2), Coronaviruses (CoVs). The largest RNA viruses identified to date belonging to the family Coronaviruses [2]. The same family also includes Severe Acute Respiratory Syndrome (SARS), and the Middle East Respiratory Syndrome (MERS). Seven identified human coronaviruses exist, containing the novel SARS-CoV-2, of such, four are (HCoV-OC43, HCoV-HKU1, HCoV-NL63, and HCoV-229E) circulated through the human population and caused mild symptoms [3].

The clinical range of SARS-CoV-2 contamination appears to be broad, encompassing asymptomatic infection, mild upper respiratory tract sickness, and severe viral respiratory pneumonia but also death, aggressive worldwide [4]. Thus, molecular tools to recognize new

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medications to prevent relapse and prolong patient survival as persistently needed to be refined.

Since COVID-19 is a significant outbreak in nearly all countries around the world, new approaches to finding such therapeutic drugs against COVID-19 are required. CoVs recombination rates are very high, because constant transcription errors evolve, and RNA Dependent RNA Polymerase (RdRP) jumps [5].

Most of these virus RNA content encodes viral polymerase, RNA synthesis materials, and two large nonstructural polyproteins (ORF1a-ORF1b), which are not involved in modulating of the host response. The remaining one-third of the genome codes for four structural proteins (spike (S), membrane (M), envelope (E), nucleocapside (N), and the helper-proteins [6].

The main protease domain (Mpro) has been documented to be a conserved target in favor of developing new inhibitors throughout the entire coronaviruses subfamily [7]. The 3 CL protease is more commonly referred to as Mpro as it has a dominant role in the replicas protein post-translational processing. Important homology of Mpros has been identified in different humans and animals in the primary amino acid sequence and 3D structure [7].

The crystal structure methodology and numerous biochemical investigations revealed that SARS-CoV S protein (spike protein) has a solid liking for binding to human ACE-2 receptors [8]. Some potential targets have been identified for drug design spike protein, protease, protein envelop, hemagglutinin esterase, membrane protein, helicase, and nucleocapsid protein have been identified [9]. Concerning structure-based drug design, molecular docking has been the most well-known approach since the early 1980s [10]. Molecular docking examines a method of providing important information on the reasoning of designing ligands for an especially active site of a significant macromolecule. This is an economical and present-day drug disclosure trend where technology base ligand-protein interaction uncovers the pre-synthesizing prospects [11]. A major type of molecular docking is protein-ligand docking duo to its therapeutic applications in new structure-based medication design. The most popular docking software's have been developed for both academic and commercial use are FlexX or AutoDock or FRED or DOCK or Glide or GOLD or QXP or ICM or Hammerhead or rDock or MCDock or SLIDE or Surflex or LigandFit and many others. [12]. Among these programs, AutoDock Vina, MOE-Dock, and GOLD predicted highst-ranking poses with best scores [16].

Protein-ligand docking is a computational process that attempts to evaluate the position, conformation, and orientation most likely to bend a ligand (often a small organic molecule) to a protein. Overall, it has recently been reported that these docking programs can estimate experimental poses with average root-mean-squared deviations (RMSDs) of 1.5 to 2 Å [13].

Guenther successfully crystallized the main protease of COVID-19, PDB-ID:6YNQ, which is now accessible to the globe, et al. [14], figure 1 shows the structure of Protein 6YNQ. Main

Protease bound to 2-Methyl-1-tetralone with three unique ligands (P6N-DMS-CL) as 2D structure, figure 2.

The docking system requires multiple main steps: estimation of the ligand conformation and its orientation and position within these locations and evaluation of the binding affinity [15]. X-ray crystallization continues to be the primary source of 3D structural data for protein targets. In favorable situations where the unknown structure proteins have high sequence homology to known structures, homology modeling can provide a viable alternative by generating a suitable starting point for the "in silico" discovery of high- affinity ligands. [16]

Many potential therapeutic molecules that include antibiotics, antiviral and anti-malarial properties are being tested against COVID-19, which has caused global devastation. Suravajhala, et al, evaluate the binding affinities of 14 drug candidates with SARS-Cov-2 proteins (PDB ID: 6VYO, 6M17, 6W4H, 6M71), they found that curcumin could play a major role in regulating the activity of nucleocapsid and nsp10, both of which are indirectly related to the detection and processing of viral RNA [17]. Atanu Barik et al. select 6LZG, 6NUR, 6W4H, and 6M71 PDB non-structure protein(NSP7,12) and identify FDA approved drug combinations [11]. Sibi Raj et al. focused on the drug repurposing against the main protease in coronavirus (6LU7) using pyRx and Autodock-Vina to recognize potent FDA approved inhibitors against COVID-19 Main Proteases [7].
Zhenming Jin et al. initiate a program of combined structure-assisted drug design, virtual drug screening, and high-throughput screening to distinguish new medication drives that target the COVID-19 virus main protease 6LU7, results exhibit the efficacy of this screening methodology, leading to the fast disclosure of medication leads with clinical potential in response to new infectious diseases. [18]

Production of new drugs is a time-consuming process, and clinical approval usually involves many years of research. This work aims to find a potential drug candidate by finding the effective binding between a small molecule (ligand) and a protein by applying protein-ligand docking for target 6YNQ Main protease (Mpro) protein, which hasn't been reported before using AutoDock Vina technique in 25 compounds. New targets and compounds are expected to meet the developing threat from COVID-19.

Figure 1, 3D structure of 6YNQ protein

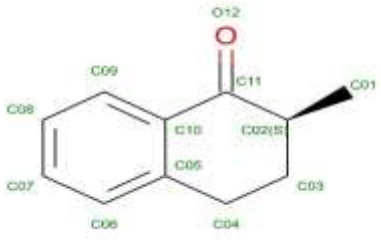


Figure 2, 2D of P6N ligand

II. MATERIALS AND METHODS

Protein–Ligand interaction provides a significant role in the design of structural-based drugs [19]. The general tasks of protein-ligand docking process of protein 6YNQ for drug discovery can be described in Figure 3.

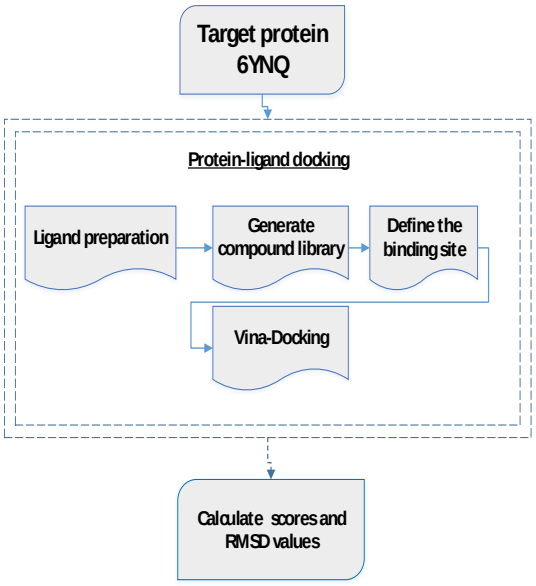


Figure 3, protein -ligand docking process

The preliminary studies done to date are not approved for the therapeutic use against COVID-19 infected patients. Liu et al. (2020) have correctly crystallized the main protease (MPro) of COVID-19, PDB-ID:6YNQ, which is now accessible globally. 6YNQ represents a potential target for the inhibition of SARS-CoV2 replication. Therefore, in our study, we identified 25 compounds out of 940 compounds as phase I, a potential inhibitor against COVID-19 major protease. These inhibitors can be repurposed against COVID-19 major protease to control the spread of Coronavirus.

1) In silico Docking:

Docking is a tool for prediction of the preformed orientation and activity of molecule to targeted protein. The molecular docking method, AutoDock Vina1.0 at Galaxy \Europe open software [Simon Bray, 2020 **Protein-ligand docking (Galaxy Training Materials)** [20], was used to predict docking and scoring of the ligands. The box center for docking was defined sufficiently enormous to the information of active sites or binding sites of its homologs of SARS-CoV [21].

A. Ligand preparation.

After download the 6YNQ protein from PDB, the next step is to separate protein and ligand (P6N) files and then convert the ligand file into SDF/MOL format using the OpenBabel with pH:7.4. The structure of the protein was saved in PDB format for further analysis. Reference molecules are (2S)-2-Methyl-3,4-dihydro-2H-naphthalen-1-one,
were downloaded from PubChem server (PubChem ID-7058063), (figure 4 shows the 3D (2S)-2-Methyl-3,4-dihydro-2H-naphthalen-1-one ligand With 160.21 g/mol molecular weight and $C_{11}H_{12}O$ molecular formula.

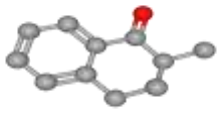


Figure 4.3D conformer of the reference compound

B. Generate compound library

We will generate our compound library by searching pubChem for compounds with a similar structure to the ligand in

the PDB file, converting the output files to SMILES format, representing the 2D structure of a molecule a chemical graph and states only the atoms and the connectivity between them.

Using Tanimoto cutoff score:80 and to filter the compound, we choose Lipinski's Rule of Five (Ro5) [22] Lipinski, commonly used in the extraction of potentially active compounds from combinatorial libraries with good oral absorption and/or permeation [23].

The Ro5 claims that poorly absorbed intestinal wall molecules have two or more of these characteristics: molecular weight above 500, the logarithm of n-octanol/water partition coefficient (ClogP) above 5 (or MlogP lower than 4.15), more than 5 hydrogen-bond (HB) donor groups (expressed as the sum of NHs and OHs groups) and more than 10 HB acceptor groups (expressed as the sum of Ns and Os atoms). Since each threshold is multiplied by 5, the rule was named Ro5 [24]. Lipinski rule of 5 assists in candidates to discern between drug-like and non-drug like. It generates a 940 compound library with a similar structure to the ligand and selects the first 25 compounds to work with for the first phase.

C. Define the binding sites

The most significant step in molecular docking is to locate the ligand-binding sites on a protein. Each compound structure needs to be converted to PDBQT format containing atom type definitions and atomic charges. Converting each compound from 2D to 3D structure and identifying the optimal binding site by Calculating the box parameters for an AutoDock Vina step, all three buffers (X,Y,Z axis) of the box set to be 5. The expected energy of the molecular field model is an element of an atomic position normally in Cartesian space [16]. For every ligand atom type, the interaction energy between the ligand atom and the receptor is determined for the whole binding site discretized through a grid. This advantage is that interaction energies do not need to be determined at each step of the docking process however just looked up in the respective grid map.

D. Protein-ligand docking

After the compounds are screened, a virtual screening environment is created through autodock vina, the output a collection containing an SDF output file for each ligand, which contains multiple docking poses and scoring files for each of the ligands.

Docking systems usually use scoring criteria, which can be seen as an attempt to estimate the methods' standard chemical potentials. The scoring function produces a score based on the ligand, which is best select. The poses of docking are ranked according to their docking scores and both the ranked list of docked ligands, and their respective binding poses may be exported.

2. Evaluation

The efficiency of docking methods in estimating a ligand binding pose is usually calculated using the RMSD. The adaptability of the system is a significant challenge in the come up with the exact pose. Autodock vina implement symmetry correction in docking RMSD computation, giving a module that makes correspondence by mapping every atom of one pose to the nearest atom of the same kind from the other pose.

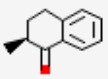
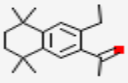
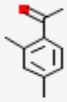
A successful output is only considered when the RMSD is smaller than 2Å [25]. Docking results were assessed with RMSD of each predicted pose versus the crystal structure. For one ligand-protein pair, when a pose is ranked as a good solution ≤ 2Å, this implies that the scoring function repeated the crystallographic binding direction.

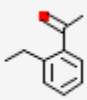
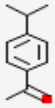
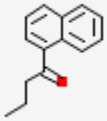
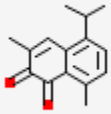
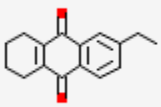
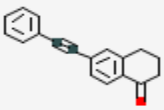
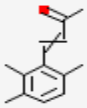
III. RESULTS AND DISCUSSIONS

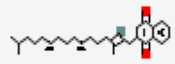
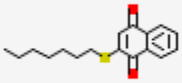
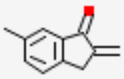
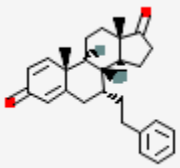
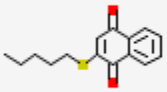
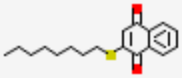
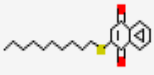
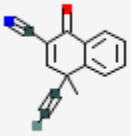
Human coronaviruses present a significant disease burden. COVID-19 is a highly contagious, high mortality disease. Several measures are needed to prevent the epidemic at a higher rate, such as early diagnosis, avoiding unnecessary panics, isolation reporting, or supportive treatments. Molecular docking is a simulation process on a computer that is widely used to predict a receptor-ligand complex conformation, where the receptor is normally a nucleic acid molecule or a protein, and the ligand can be another protein or a small molecule. Some researchers have been performed out on COVID-19 using molecular docking, trying to discover vaccines and drugs to control this virus.

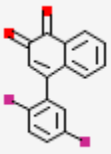
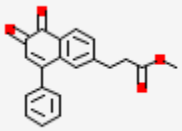
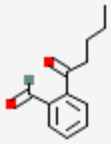
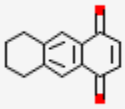
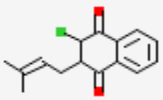
In this study, protein-ligand docking was applied to the development process and drug discovery to find a potential drug candidate. Docking and scoring of the first set of compounds 25 out of 940 to the MPro protein (6YNQ) using AutoDock vina for the first phase to get the best score and the lowest RMSD for the chosen compounds, RMSD is an indicator of the stability of ligand-protein complexes. A compound with lower RMSD is preferred as a possible drug candidate. Table 1. Summarizes ranked compounds screened against covid-19 Mpro receptor binding site with their respective structures, interacting residues, binding affinity and, docking score.

Table 1.25 compounds information

PubChem CID	Compounds name	Compound structure	Docking score	RMSD
7058063	(2S)-2-methyl-3,4-dihydro-2H-naphthalen-1-one		-5.6	1.753
6930	Versalide		-6.6	1.067
6985	2',4'-Dimethylacetophenone		-4.9	1.926

16503	2'-ETHYLACETOPHENONE		-4.9	2.708
16504	2-Isopropylacetophenone		-5.1	2.797
12578	4-ISOPROPYLACETOPHENONE		-5.3	2.873
16506	1-(2,6-dimethylphenyl)ethanone		-4.6	2.468
17890	1'-BUTYRONAPHTHONE		-5.9	1.689
21742	Mansonone C		-6.2	3.425
27376	6-Ethyl-1,2,3,4-tetrahydroanthraquinone		-6.3	2.885
53321027	6-(phenylethynyl)-3,4-dihydronaphthalen-1(2H)-one		-5.9	0.909
53426133	4-(2,3,6-TRIMETHYLPHENYL)-3-BUTEN-2-ONE		-6	1.78

56927684	2-Phytyl-1,4-naphthoquinone		-5.2	1.697
57411027	1,4-Naphthalenedione, 2-(heptylthio)-ACMC-20lmnz		-5.9	2.85
58198133	2-Methylene-6-methylindan-1-one		-5.6	1.94
68668617	7alpha-Phenethylandrosta-1,4-diene-3,17-dione		-7.7	2.219
71324516	1,4-Naphthalenedione, 2-(pentylthio)-ACMC-20lmnx		-5.6	2.607
71324517	1,4-Naphthalenedione, 2-(octylthio)		-5.9	1.648
71654397	2-DECYLSULFANYLNAPHTHALENE-1,4-DIONE		-5.5	2.373
122177483	4-ETHYNYL-4-METHYL-1-OXONAPHTHALENE-2-CARBONITRILE		-5.9	2.6

44301154	4-(2,5-Difluorophenyl)-1,2-naphthoquinone		-8.2	1.533
44301245	5,6-Dioxo-8-phenyl-5,6-dihydronaphthalene-2-propionic acid methyl ester		-7.6	1.771
44431358	2-pentanoylbenzaldehyde		-5.5	2.042
44582382	5,6,7,8-tetrahydroanthracene-1,4-dione		-7.3	0.027
45269651	3-chlorodeoxylapachol		-7	2.146

The best scores and RMSD compounds that can be detected are: 4-(2,5-Difluorophenyl)-1,2-naphthoquinone, Versalide, 4-(2,3,6-TRIMETHYLPHENYL)-3-BUTEN-2-ONE, 5,6-Dioxo-8-phenyl-5,6-dihydronaphthalene-2-propionic acid methyl ester, 1,4-Naphthalenedione, 2-(octylthio), and 5,6,7,8-tetrahydroanthracene-1,4-dione with red color as in figure 5. The compounds are approved by FDA to be used as potential drugs.

1- 4-(2,5-Difluorophenyl)-1,2-naphthoquinone compound : according to drug bank web [26]. The Nintedanib is a small molecule kinase inhibitor utilized in pulmonary fibrosis treatment, systemic sclerosis-associated interstitial lung disease, and non-small cell lung cancer (NSCLC). On April 6 2011, the FDA approved vandetanib to treat adult patients with nonresectable, locally advanced, or metastatic medullary thyroid cancer.

2- 4-(2,3,6-TRIMETHYLPHENYL)-3-BUTEN-2-ONE: according to drug bank web [27] : Streptococcus pneumoniae type 6b capsular polysaccharide diphtheria crm197 protein conjugate antigen is a sterile vaccine.

3- 5,6,7,8-tetrahydroanthracene-1,4-dione: according to drug bank web [27]. Nifedipine is an inhibitor of L-

type which reduces the pressure of the blood and increases the supply of oxygen to the heart, Loxapine, a dibenzoxazepine compound used in schizophrenia.

4- 1,4-Naphthalenedione, 2-(octylthio): according to the drug bank web [28]. A potent, non-nucleoside reverse transcriptase inhibitor (NNRTI) used in combination with nucleoside analogues for the treatment of Human Immunodeficiency Virus Type 1 (HIV-1) infection and AIDS, Cefradine;is a semi-synthetic cephalosporin antibiotic.

5- Versalide: according to drug bank web [29]. Bordetella pertussis toxoid antigen (formaldehyde inactivated) is a vaccine. Protein C is an endogenously occurring plasma protein that plays a key role within the coagulation cascade. Protein C is a zymogen, or enzyme precursor, of a vitamin K-dependent anticoagulant glycoprotein (serine protease) synthesized in the liver.

Table 2 summarizes the selected RMSD compounds with suggested drugs and other existing work. All of the mentioned studies apply Autodock Vina [11,20,24,31] for COVID-19 infection that confirms the advantages of applying Autodock Vina due to its higher precision in estimating ligand-protein interaction compared to the previous version of AutoDock [24], also (1) it offers great accuracy in predicting ligand-protein interaction contrasted with its past AutoDock 4.2 (2) it offers more limited time due to its multiple core processors (3) it offers more precision for ligand processing more than 20 rotatable bonds. So this study can be used to find some novel compounds against COVID-19 disease.

Figure 5 shows the 3D protein structure with the prediction of Mpro enzyme using NGLViewer tool the obtained findings may motivate scientists working on the 6YNQ protein, which can help in drug discovery.

Table 2 summarize suggested drugs with related work

PDB code	Drugs	Drug discovery technique
6YNQ	1- Nintedanib 2- Nifedipine 3- NNRTI 4- Bordetella pertussis toxoid antigen	Molecular docking(AutodocKVina)
6LU7	1- cinanserin	Molecular docking (Glide, iFitDock) [29]
6LU7	1- Nelfinavir 2- Rhein 3- Withanolide 4- Aloe-emodin	Molecular docking (AutodockVina) [7]
6LU7	1- oseltamivir 2- ritonavir 3- remdesivir 4- Chloroquine 5- Hydroxychloroquine	Molecular docking(AutodocKVina) [21]
2GZ7	1- K-252a 2- Quinfamid 3- Mdl-29951	Molecular docking (AutoDockVina) [30]

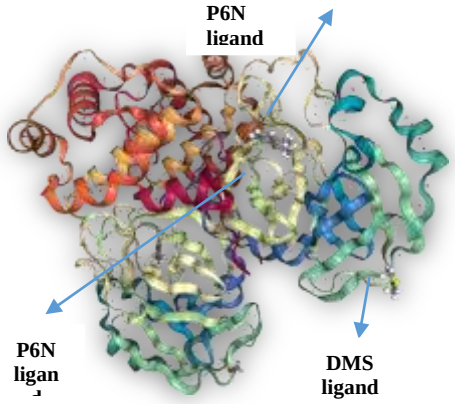


Figure 5 -3D protein with all 3 ligands with base

Two docking poses for a ligand-bound(P6N) to the active site of 6YNQ.

One (docking score -7.3) can be seen to be bound deeper in the active site than the other (docking score -4.5), which is reflected in the difference between the docking scores using NGL viewer Figure 6.

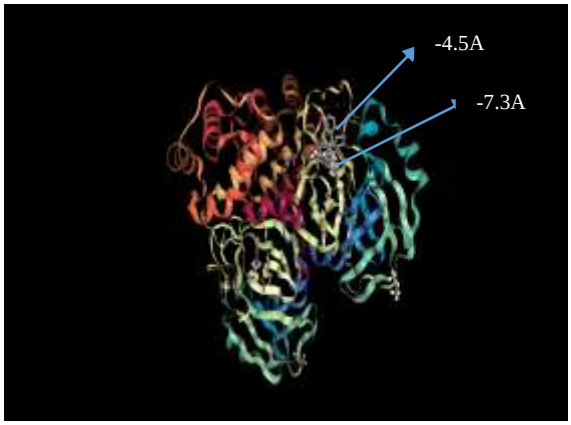


Figure 6, Two docking poses for a ligand bound to the active site of 6YNQ.

IV. CONCLUSIONS

Since late December 2019, another epidemic outbreak has risen up out of Whuhan, China. Rapidly the new coronavirus has spread worldwide. Nuclear magnetic resonance spectroscopy strategies, high-throughput protein purification, and crystallography have been developed, and contributed to many structural details of proteins and protein–ligand complexes.

The use of complementary observational and informatics methodologies raises the chance of success in several phases of the research process, from identifying novel targets and elucidating their functions to discovering and developing lead compounds with desired characteristics. There is no vaccine or compelling treatment able to avoid the Novel Coronavirus (COVID-19) infection.

Docking plays a crucial role in the drug design and discovery process. The present study was carried to discover novel inhibitor molecules against Mpro receptor. Consequently, a library of protein data bank from Research Collaboratory for Structural Bioinformatics (RCSB) was PDB analyzed by molecular docking techniques. The 25 compounds' results were analyzed and compared with reference molecules of protein which demonstrates that these compounds can bind more efficiently and act as inhibitors. The best score and RMDS compounds we can detect are: 4-(2,5-Difluorophenyl)-1,2-naphthoquinone , Versalide, 4-(2,3,6-TRIMETHYLPHENYL)-3-BUTEN-2-ONE, 5,6-Dioxo-8-phenyl-5,6-dihydronaphthalene-2-propionic acid methyl ester, 1,4-Naphthalenedione, 2-(octylthio), and 5,6,7,8-tetrahydroanthracene-1,4-dione.

The detection of a protein –ligand docking is the most interesting finding when matching the high score compounds with drug bank. It revealed that some drugs (Nintedanib, Nifedipine, NNRTI , and Bordetella pertussis toxoid antigen) could be effective treatments for COVID-19 infection. Finally, this study concludes that compounds can be utilized as potential antiviral candidates. These novel molecules could be utilized for further innovation and development of antiviral compounds against Coronavirus. Results of protein –ligand docking motivate us to try out more compounds that could represent possible solutions in critical areas of human health and take advantage of the current findings related to COVID-19 drug design.

Different evaluation method criteria or docking algorithms will improve the scoring, ranking, and docking techniques. Experimental technology still relies on realistic interactions between small molecules and receptors.

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