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SARS-COV-2 Proteins, in Complex with Tirilazad

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Abstract— In this study, our approach was to carry out a complete investigation of molecular docking analysis with the major SARS-CoV-2 proteins. We analysed more than 6000 drugs, downloaded by the PubChem database. Particular attention, we have focused on Spike Glycoprotein and Main protease $3CL^{pro}$ Covid-19 proteins, by "Blind docking" method and "Selective docking" procedure, in Ligand Binding site, with AutoDock Vina using Pyrx software. From our results, we have selected Tirilazad against COVID-19. In fact, it reported having an excellent ability to bind both with the "Native Spike Glycoprotein", with a Binding Energy of -11.8 kcal mol^{-1}, and with the South African (B.1.351) SARS-CoV-2 spike protein variant, with a Binding Energy -10 kcal mol^{-1}. Indeed, in the second case, the docking analysis was evaluated in the active area of three key amino acids belonging to the Spike Protein RBD, responsible for a higher binding with the ACE2 receptor. They are ASN 417, Lys 484, and Tyr 501 respectively. In addition, Tirilazad has shown a Binding energy score of approximately -10.5 kcal mol^{-1} against SARS-COV-2 Main protease. This has led us to conclude that this drug could be an excellent candidate against Coronavirus (COVID-19) pandemic, even though further in vitro and in vivo studies are needed.

Keywords— Tirilazad; SARS-COV-2

I. INTRODUCTION

COVID-19 disease caused by an infection of the SARS-CoV-2 virus, known as novel coronavirus or 2019-nCoV, was identified in December 2019 [1]and resulted in more than 3,000,000 deaths as of April 25 2021 (WHO https://covid19.who.int/, 2021)[2]. Symptoms of COVID-19 are variable, but often include fever, cough, fatigue, breathing difficulties, nausea or vomiting and loss of smell and taste [3, 4]. The risk of morbidity and mortality from COVID-19 increases significantly in the presence of coexisting medical conditions. COVID-19 is characterized by severe pneumonia and approximately 20% of infected persons develop a severe form which gives rise to respiratory failure that requires intensive and sub-intensive therapy [5,6]. It has been shown that this type of virus can cause severe respirators for humans, especially in some by causing widespread alveolar damage [7]. Four main sub-groupings of coronaviruses, alpha, beta, gamma, and delta, are known [8]. The viruses that cause the most serious infections are severe acute respiratory syndrome (SARS), which was caused by SARS-CoV in 2002, [9,10], Middle East Respiratory Syndrome (MERS), which was caused by MERS-CoV in 2012 [11] and SARS-CoV-2 which causes the disease COVID-19 [12,13].

Another important SARS-COV-2 protein studied in this work is the viral 3-chymotrypsin-like cysteine protease ($3CL^{pro}$), also termed M-^{Pro}, a polypeptide of 306 amino acids, which plays a key role in the replication of coronavirus. The $3CL^{pro}$ is the main protease found in coronavirus. For this reason, it is a potential drug target for anti-SARS-CoV-2 drug development [14, 15]. Several studies have recently been published that demonstrate its effectiveness against SARS-COV-2. Remdesivir (Veklury), is an approved drug by the U.S. Food and Drug Administration (FDA) and it inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2. Veklury is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor [16]. Several studies reported different drugs to fight this viral disease: Hydroxychloroquine [17], Dexamethasone [18], Imatinib [19], Nelfinavir [20], Heparin [21] , Favipiravir [22] and Arbidol [23] . A positive effect of low density Heparin [24], of some antiviral drugs for instance Ritonavir and Lopinavir [25] and the glucocorticoids, for instance Dexamethasone [18], against severe COVID-19 disease. In this work, we used a virtual screening approach to identify potential candidates towards SARS-CoV-2 proteins.

Nowadays Cheminformatics, widely used in Drug Discovery it refers to the use of physical chemistry theory with computer and information science techniques—so-called "in Silico" techniques.

II. RELATED WORK

This computational study aims to find a potential anti-COVID-19 drug that has an excellent ability to bind with Coronavirus proteins.

III. METHODOLOGY

Parameters Docking for SARS-CoV-2- main replicase-protease (The crystal structure of COVID-19 main protease in complex with an inhibitor N3)

ID PDB 6LU7 Chain A: Center X (= -10.80); Centre Y (=12.60); Centre Z (=69.01); Dimensions (Angstrom) (Å) X, Y, Z [= 25.45;25.00, 29.28]; exhaustiveness = 8
Parameters Docking for SARS-CoV-2- "Native Spike Glycoprotein" (Structure of the SARS-CoV-2 spike glycoprotein (closed state)

ID PDB 6VXX Chain A, B, C: Center X (= 210); Centre Y (=210); Centre Z (=207.37); Dimensions (Angstrom) (Å) X, Y, Z [= 119.07; 125.29, 158.58]; exhaustiveness = 8
Parameters Docking for SARS-CoV-2- (South African (B.1.351) SARS-CoV-2 spike protein variant (S-GSAS-B.1.351) in the 1-RBD-up conformation)

ID PDB 7LYN Chain A: Center X (= 150.19); Centre Y (=167.31); Centre Z (=96.63); Dimensions (Angstrom) (Å) X, Y, Z [= 79.9773.20, 47.44]; exhaustiveness = 8
It must be taken into account that both the protein and ligands preparation phase are crucial to have an evaluation as authentic as possible of the interaction process of the Protein-Ligand complex. These phases were optimized before docking, using AutoDock Vina [27].
Software used for Docking for the characterization of proteins

- PyRx (https://pyrx.sourceforge.io/downloads) PyRx [28] is a Virtual Screening software for Computational Drug Discovery that can be used to screen libraries of compounds against potential drug targets. This Software was used to calculate Autodock Vina Function Score for SARS-COV-2 proteins.

-AMDock (Assisted Molecular Docking) is a user-friendly graphical tool to assist in the docking of protein-ligand complexes using Autodock Vina and AutoDock4. AMDock integrates several external programs (Open Babel, PDB2PQR, Auto Ligand, ADT scripts) to accurately prepare the input structure files.(https://github.com/Valdes-Tresanco-MS) [29].

- BIOVIA Discovery Studio Visualizer [30] (https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery studio/visualization/#:~:text=The%20BIOVIA%20Discovery%20Studio%20Visualizer%20is%20a%20free%2C,without%20loss%20of%20either%20time%20or%20scientific%20information), was used for 2D diagram of the receptor ligand complex, from Results of Docking by Autodock Vina and Autodock 4.

LIGPLOT Software [31] (https://www.ebi.ac.uk/thornton-srv/software/LIGPLOT/manual/) was used for 2D diagram of the receptor ligand complex, from Results of Docking by Autodock Vina and Autodock 4.

IV. RESULTS AND DISCUSSION

The primary focus of this Virtual screening (VS) study is to search for a commercial drug with low toxicity and minimally invasive, with its oral administration or a biologically active molecule, against one or more SARS-COV-2 proteins.

VS has been defined as the "automatically evaluating very large libraries of compounds" using computer programs, for instance in this work Pyrx software was used [28].
The first step of this milestone goal, we have set, was a bibliographic investigation of most of the drugs reported in Literature.

Specifically, we took as a reference known Database "PubChem", which is an open chemistry database at the National Institutes of Health (NIH). (https://pubchemdocs.ncbi.nlm.nih.gov/about).
It mostly contains millions of small molecules, many drugs, and all related compounds used in SARS-CoV-2 clinical trials.

In this present work, about 50 drugs were selected among the most studied ones, downloaded from (https://pubchem.ncbi.nlm.nih.gov/#tab=compound&query=covid-19%20clinicaltrials) and evaluated through the Docking analysis, estimated by the AutoDock 4 function score with the AMDock software [29] against SARS-COV-2 M-^{pro}, in its active site.

In this way, we have estimated their free Binding Energies and their values of the constant Ki, in order to better understand which of these binds it better or worse against this type of viral protein. All information on the respective drugs currently studied against COVID-19 is available on the PUBCHEM Database (https://pubchem.ncbi.nlm.nih.gov/).

From results of Docking, we found out that Lopinavir, Nelfinavir, Opaganib, Bemcentinib, Imatinib, and Dexamethasone have a High Binding Energies score of ca -10 kcal/mol, comparable to the Crystalized Ligand Telaprevir, onto in the Active site of the M-^{pro} protein.
Moreover, they have excellent estimation inhibitory constant (Ki) values in the order of 25-30 nanomolar, demonstrating that they could potentially be excellent candidates for fighting this virus. (See Table 1) .

The following step was to search, by Structure-based Virtual Screening, an alternative drugs, rather than those that are widely discussed in the literature, (See below Table 1), in order to give similar or better results both in terms of Estimation of Ki (in nM Units) and Binding Energy (kcal mol $^{-1}$)

To accomplish this Target, we have built a large library of ca 6000 drugs, calculated by AutoDock Vina through Pyrx Software [28]. For this goal, Tirilazad drug, a corticosteroid hormone has shown a Binding energy score of approximately -10.5 kcal mol^{-1} against SARS-COV-2 Main protease, in Ligand Binding Active Site. (See figure 1).

As reported in Literature, Tirilazad has been used in trials studying the treatment of Spinal Cord Injury [32] and it is demonstrated for Neuroprotection [33].

The second docking methodology, which we present for the first time was to calculate the Binding Energy of this proposed drug in Unmodified spike protein (PDB 6VXX), by "Blind docking" approach, considering all the viral protein in the complex and quantifying the ability of this drug to bind to it. In this way, Tirilazad has reported a high Binding Energy score of about -11.8 kcal mol-1 (See below figure 2). In addition, we calculated its "Vina Score" in the South African (B.1.351) SARS-CoV-2 spike protein variant in the active area of three key amino acids belonging to the Spike Protein RBD, responsible for a higher binding with the ACE2 receptor. They are ASN 417, Lys 484, and Tyr 501 respectively. From AutoDock Vina analysis Tirilazad has obtained a -9.9 kcal mol^{-1}value (See below figure 3).

Table 1. Molecular Docking, of Investigated Drugs in Literature , in Ligand Binding Site on 3CL pro (PDB 6XQS) of SARS-CoV-2, Calculated by AutoDock 4 (Lamarckian genetic algorithm, LGA) with AMDock. (https://pubchem.ncbi.nlm.nih.gov/#query=covid-19).

Drugs	**Binding Energy (kcal mol^{-1})**	**Estimated Ki**	**Ligand efficiency (kcal mol)**
Abivertinib	-8,95	275,18 nM	-0,25
Acalabrutinib	-8,1	1,16 µM	-0,23
Ambroxol	7,72	2,19 µM	-0,43
Anakinra	-6,3	24,14 µM	-0,19
Apremilast	-8,2	975,81 nM	-0,26
Arbidol	-8,16	1,04 µM	-0,28
Azithromycin	-8,41	684,6 nM	-0,16
Baricitinib	-8,22	943,42 nM	-0,32
Bemcentinib	-10,97	9,10 nM	-0,29
Boceprevir	-9,3	152,43 nM	-0,25
Brensocatib	-8,89	340,50 nM	-0,29
Brequinar	-6,88	9,06 µM	-0,25
Cenicrivoc	-6,13	32,11 µM	-0,12
Chloroquine	-7,14	5,84 µM	-0,32
Ciclesonide	-9,59	98,43 nM	-0,25
Cobicistat	-8,25	896,84 nM	-0,15
Darunavir	-8,5	588,12 nM	-0,22
Dexamethasone	-9,59	98,43 nM	-0,34
Elbasvir	-8,81	348,53 nM	-0,14
Favipiravir	4,53	0,48 mM	-0,41
Fingolimod	-5	0,22 mm	-0,23
Galidesivir	-6,44	19,03 µm	-0,34
Hydroxychloroquine	-6,57	15,29 µM	-0,29
Ifenprodil	-8	1,37 µM	-0,33
Imatinib	-10,39	24,22 nM	-0,28
Ivermectin	-8,8	354,46 nM	-0,14
Lopinavir	-9,85	60,24 nM	-0,21
Nafamostat	-8,64	464,35 nM	-0,33
Narlaprevir	-8,29	835,29 nM	-0,17
Nelfinavir	-10,42	23,02 nM	-0,26
Opaganib	-10,27	29,64 nM	-0,38
Otamixaban	-9,02	244,51 nM	-0,27
Relacatib	-9,25	165,85 nM	-0,24
Remdesivir	-7,83	1,82 µM	-0,19
Ribavirin	-4,68	0,37 mM	-0,28
Ritonavir	-9,03	240,42 nM	-0,18
Ruxolitinib	-8,69	426,77 nM	-0,38

Selinexor	-6,27	25,36 µM	-0,2
Thalidomide	-7,26	4,77 µM	-0,38
Triazavirin	-5,6	78,56 µM	-0,37
Vidofludimus	-9,39	3,83 µM	-0,28

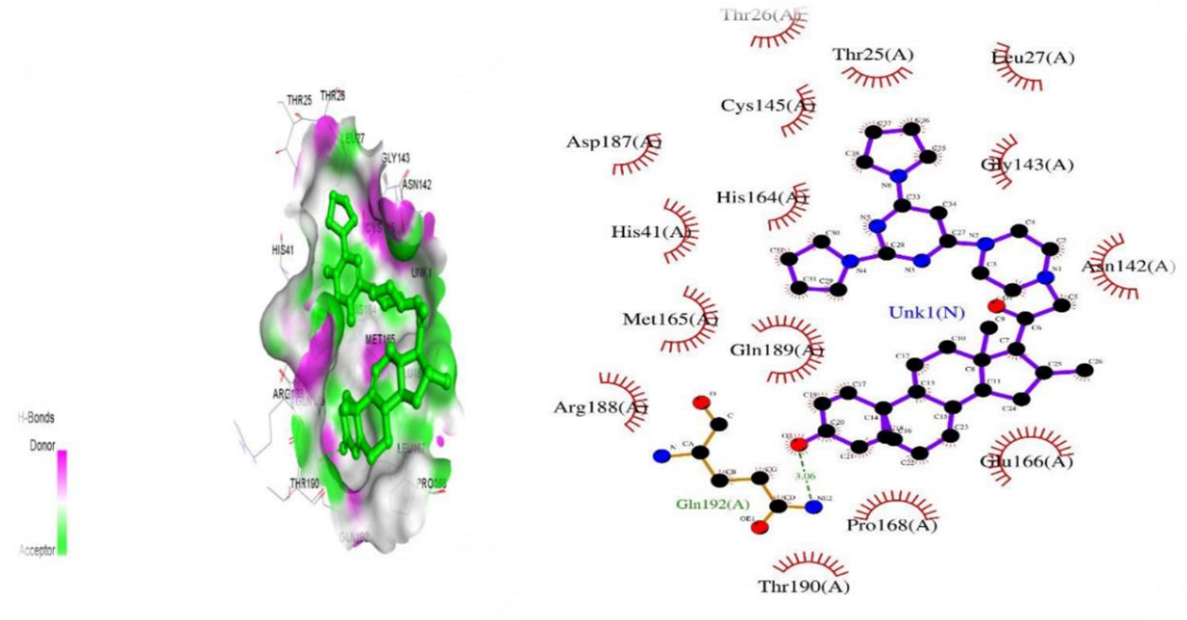

Figure 1. a) Docking crystal structure of 3D COVID-19 main protease (PDB 6lu7), in complex with Tirilazad and b) 2D Diagram residues interactions in complex with docked best pose of Binding Energy about -10.5 kcal mol^{-1} of Tirilazad drug, estimated by AutoDock Vina with Pyrx Software) 2D Diagram was reproduced by LIGPLOT software.

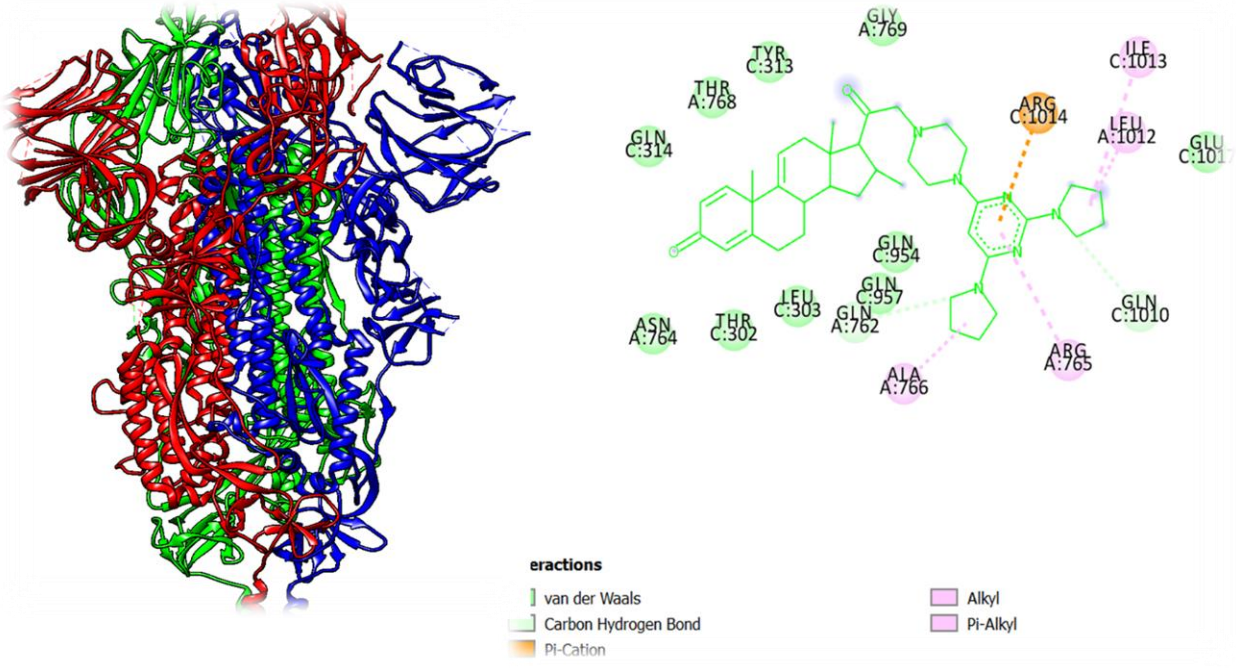

Figure 2. a) Blind Docking 3D crystal structure of Spike Glycoprotein (PDB 6VXX) and b) 2D Diagram residues interactions in complex with Docked best pose of Binding Energy about -11.8 kcal mol^{-1} of Tirilazad drug, estimated by AutoDock Vina with Pyrx Software.

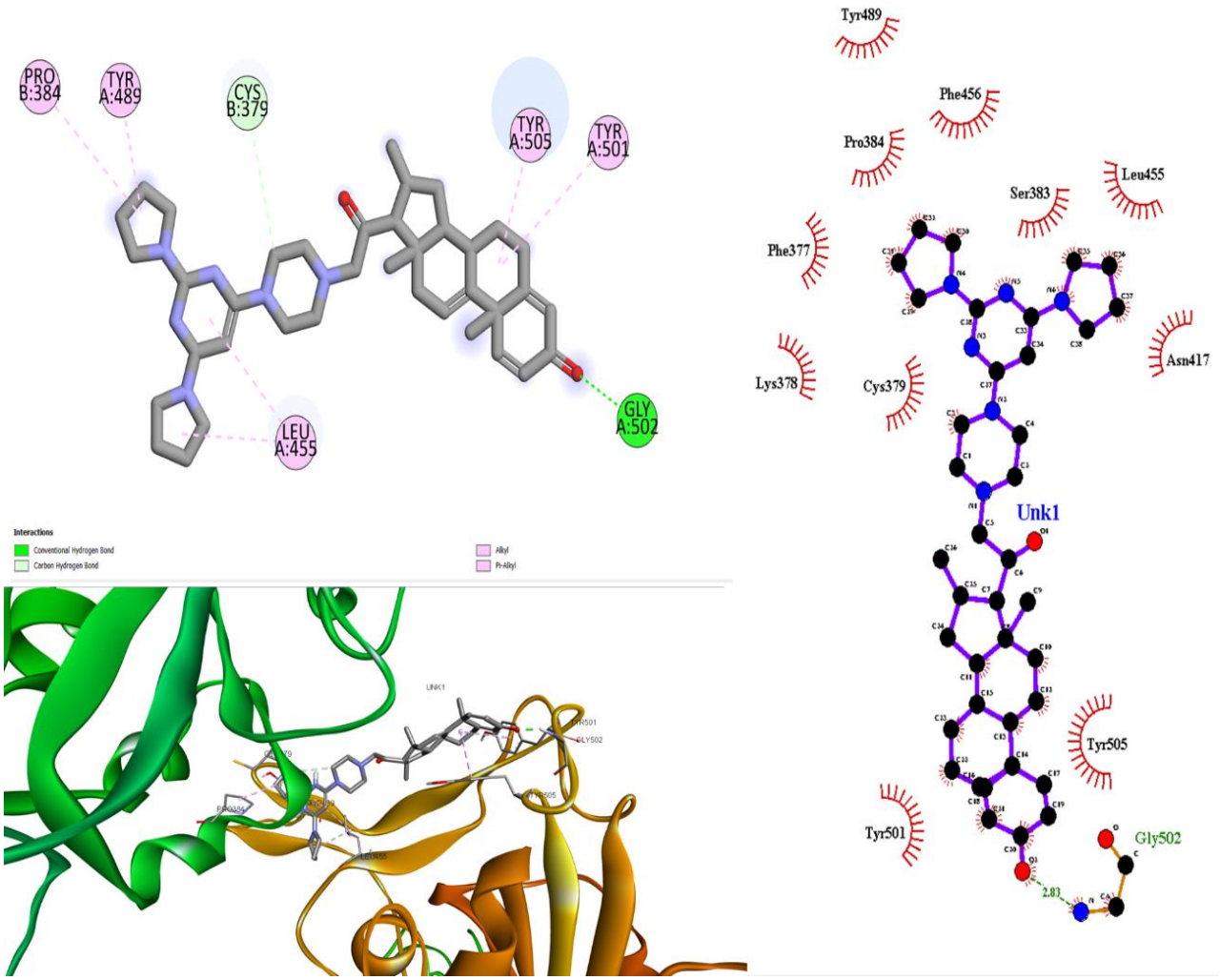

Figure 3. a) 3D Structure SARS-CoV-Spike RBD (PDB 7LYN) , in complex with Docked Tirilzad and2 D Schematic representation of hydrophobic interaction and hydrogen bonding from docking analysis of Tirilazad (-9.9 kcal mol $^{-1}$), on key amino acids (Asn 417; Lys 484, e Tyr 501) of SARS-COV-2 SPIKE RBD chain A, B, C, by Autodock Vina, with Pyrx Software.
b) 2D diagram were reproduced by Discovery Studio Biovia and LIGPLOT software.

V. CONCLUSIONS

In this work, for the first time, we present a complete investigation of Molecular Docking analysis on all the major SARS-CoV-2 proteins. Herein, we analysed more than 6000 drugs, downloaded by the PubChem database. Particular attention, we have focused on both Spike Glycoprotein and 3CL^{pro} Covid-19 protein, by blind docking method and selective docking procedure, in Ligand Binding site, with AutoDock Vina using Pyrx software and with AutoDock 4 using AMDock Software.

First all, from docking our initial results, we have selected about 30 proposed drugs, studied in Literature, with a high-affinity of Binding score (about- 9.7-12 kcal/mol).
Next, carrying out docking Validation methods, has led us to select, we selected only one proposed drug potentially active, in the Ligand Binding site pocket, of 3CL-pro SARS-CoV-2 protein .

Moreover, it reported having an excellent ability to bind both with the "Native Spike Glycoprotein", that is before undergoing mutations, with a Binding Energy of -11.8 kcal mol^{-1}, and with the South African (B.1.351) SARS-CoV-2 Spike protein variant, with a Binding Energy about -10 kcal mol^{-1}.

This has led us to the conclusion that Tirilazad could be an excellent candidate drug against SARS-COV-2, even though further in vitro and in vivo studies are needed.

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