An in-silico evaluation of COVID-19 main protease with clinically approved drugs

Project report submitted to
Visvesvaraya National Institute of Technology, Nagpur
in partial fulfillment of the requirements for the award of
the degree

Bachelor of Technology
in
Chemical Engineering

by

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Declaration

We, **PAVAN IDHOLE (BT17CME047), ZEESHAN (BT18CME043), JYOTI YADAV (BT18CME096),** hereby declare that this project work titled "**An in-silico evaluation of COVID-19 main protease with clinically approved drugs**" is carried out by us in the Department of Chemical Engineering of Visvesvaraya National Institute of Technology, Nagpur. The work is original and has not been submitted earlier whole or in part for the award of any degree at this or any other Institution.

Date:

Sr.no	Enrollment no.	Name	Signature
1	BT17CME047	PAVAN IDHOLE	
2	BT18CME029	ZEESHAN	
3	BT18CME089	JYOTI YADAV	

Certificate

This to certify that the project titled "**An in-silico evaluation of COVID-19 main protease with clinically approved drugs**", submitted by **PAVAN IDHOLE (BT17CME047), ZEESHAN (BT18CME029), JYOTI YADAV (BT18CME089)** in partial fulfillment of the requirements for the award of the degree of **Bachelor of Technology in Chemical Engineering**, VNIT Nagpur. The work is comprehensive, complete and fit for final evaluation.

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ABSTRACT

Various computer-aided to drug design (CADD) approaches are valuable assets for efficiently supporting quantitative screening by enriching chemical collections with molecules that have required features and so lowering the number of physical samples to be tested.

Initially large number of molecules are screened against a target and after each step the number of effective molecule/ligands reduce and finally either we get a drug which is FDA approved or there is a failure in drug manufacture.

We had selected a protease of sarcov-2 and screened it against several drug which are available. The screening was done by a docking software called Swiss dock available on Swiss Drug Design. The values computed in software gave values of namely clusters, binding energy, length.

An access to PDB bank was required to get SMILES, structure and different data base for each molecule.

Swissadme software was used for drug likeness which gives different properties like GI adsorption, bioavailability radar, boiled egg, etc.

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NOMENCLATURE

WHO - World Health Organization

PHEIC - Public Health Emergency of International Concern

SARS-CoV - Severe Acute Respiratory Syndrome Virus

MERS-CoV - Middle East Respiratory Syndrome Virus

SARS-CoV-2 - Severe Acute Respiratory Syndrome Cornonavirus-2

COVID-19 - Coronavirus Disease 2019

Mpro - 3 CL Protease/3-Chymotrypsin-Like protease

MM - Molecular Mass

PDB - Protein Data Bank

MD - Molecular Dynamics

ADMET - Absorption, Distribution, Metabolism, Excretion and Toxicity

LD50 Lethal dose, 50%

P-gp - P-glycoprotein

GI - Gastrointestinal

BBB - Blood Brain Barrier

INDEX

CHAPTER 1

1.1 INTRODUCTION

After COVID-19, the virus outbreak took place in mid-2020. It mainly affects respiratory system and hence it was considered a pandemic and a global threat. We have mainly two genes SARS-CoV and SARS-CoV 2. In this paper we will discuss how we screened different drug which were earlier available to this SARS-CoV-2. We have named this genome as Mpro. Mpro is critical in replicating and hence we have inhibited or suppress it.

The crystal structure of this resembles N3 inhibitor. The N3 inhibitor closely resemble to our target and is present in small intestine and works by breaking down protein and this is what the covid virus does in respiratory system.

This SARS-CoV-2 is 80% different from SARS-CoV so comes the need for new inhibiters to designed. Inhibiting this target will lead to stop in its spread.

Our goals are divided into three categories: domain I, domain II, and domain III. PDP provided us with the target's 3-D structure (protein data bank). Water molecules were removed and H2 was added as a modification. Calculated binding energy was found for two drugs and a relative comparison was carried out explaining which is better effective for SARS-CoV-2. The crown shape we see is the polyprotein on the outer surface of the virus or protease.

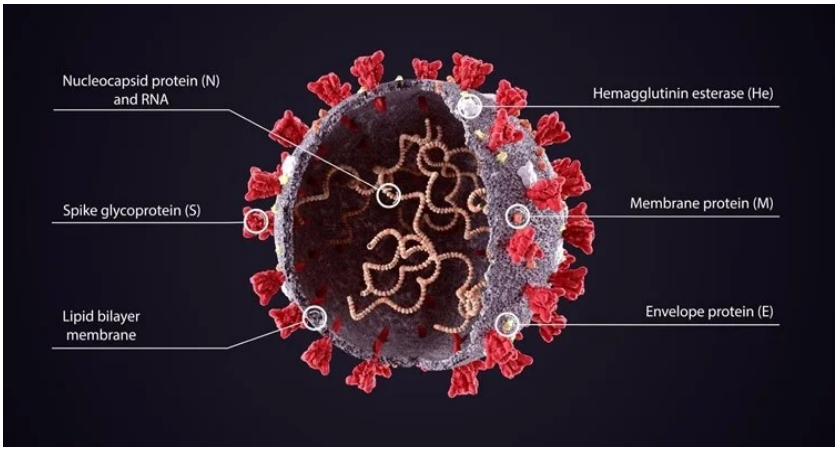

Fig.1. Crown Shape Of SARS-COV-2

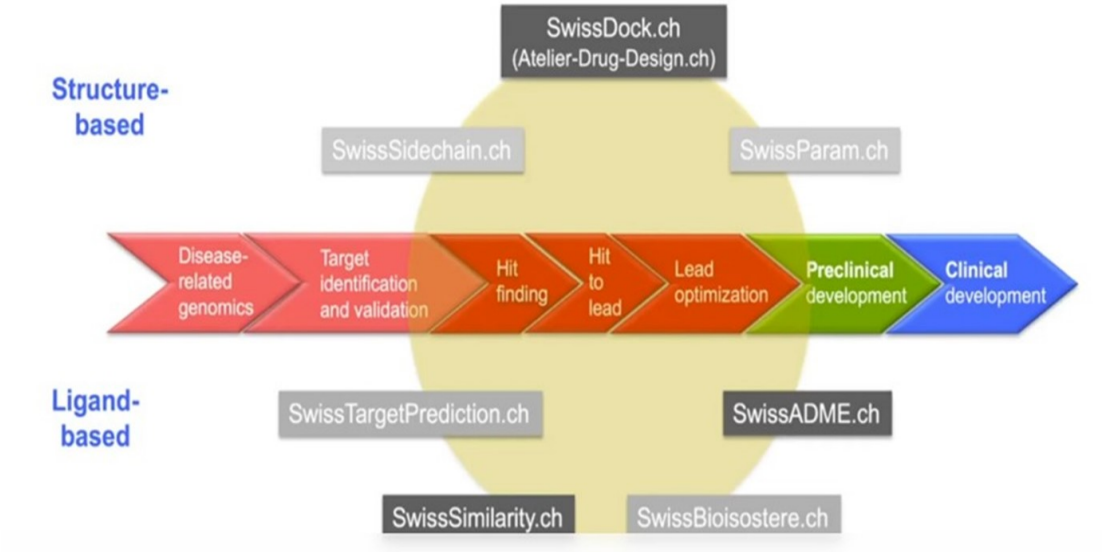

Fig. 2. Hierarchy of software process

Above figure represents the hierarchy of the software swiss drug design uses. As we can see we start with large number of drugs as potential drug but in the end, we get very a smaller number of clinically approved drug.

CHAPTER 2

METHODS

2.1. TARGET AND LIGAND RETRIEVAL FORM DATABASE

This study is descriptive and analytical. This study looked at the interactions of certified drugs. A total of 8 substances were evaluated using COVID-19 main protease (Mpro).For comparison, the N3 compound was used as a docking target.

A Drug library database was utilized to collect structural information for chosen drugs The three-dimensional structure of Mpro was retrieved in Protein Data bank (PDB). It is a compound formed by the enzyme and its inhibitor, N3. Several stages are involved in preparing the 6lu7 structure, including removing all water molecules, using a N3 inhibitor, and adding hydrogens. For docking analysis, the new file was stored.

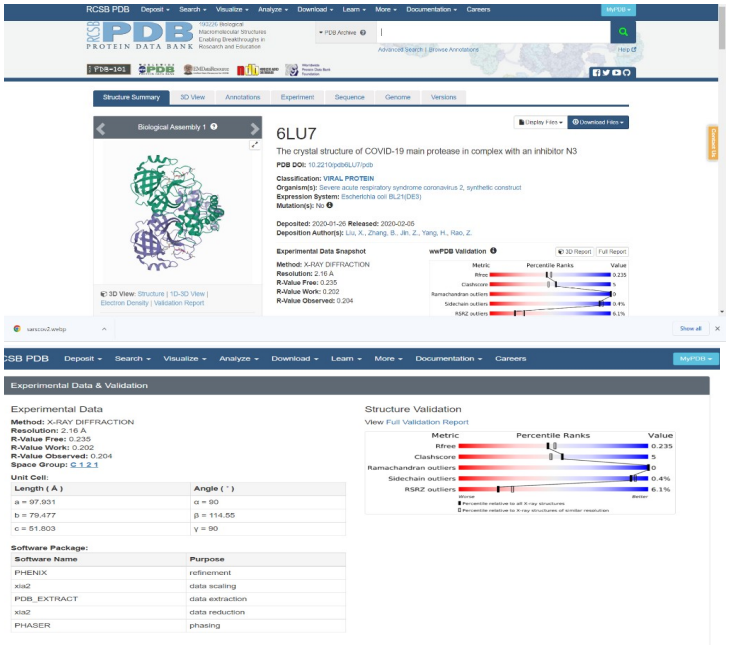

FIG.3. PDB Databank

2.2. SWISSADME

We got results with varied attributes after adding the smiles (simple molecule input line entry system).

We used four different medications to combat Sar-Cov-2.

1. Chloroquine
2. Indinvir
3.Lymecycline
4.Mizolastine

We can see the results over here also the boiled egg structure of these compounds.

A. **Chloroquine**

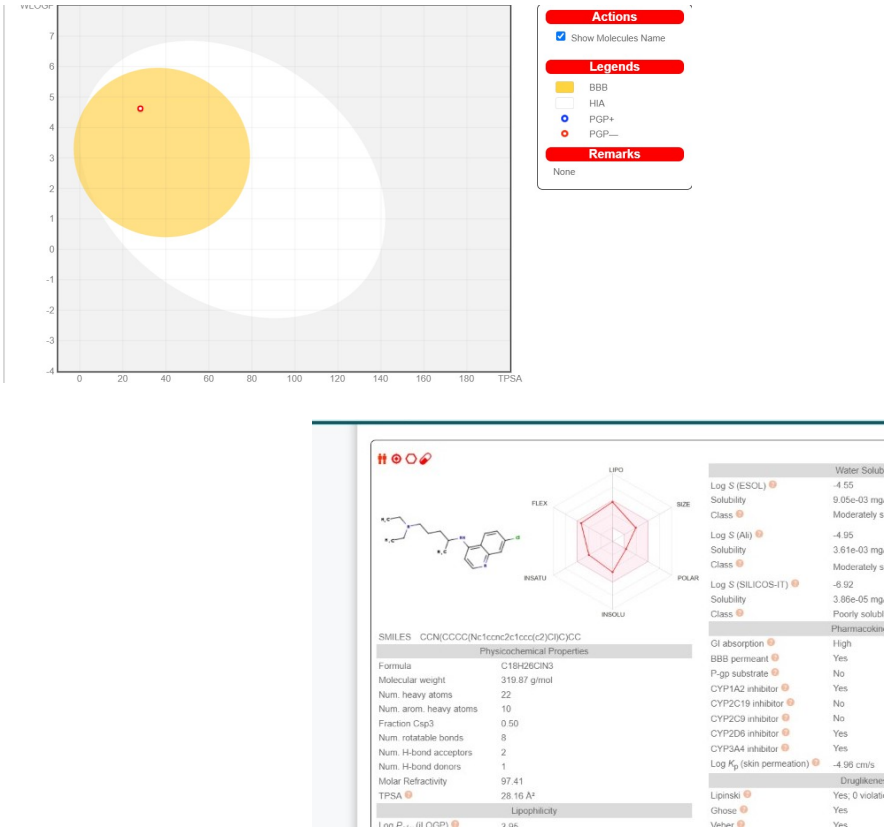

Fig.4. Chloroquine boiled structure

B. Indinavir

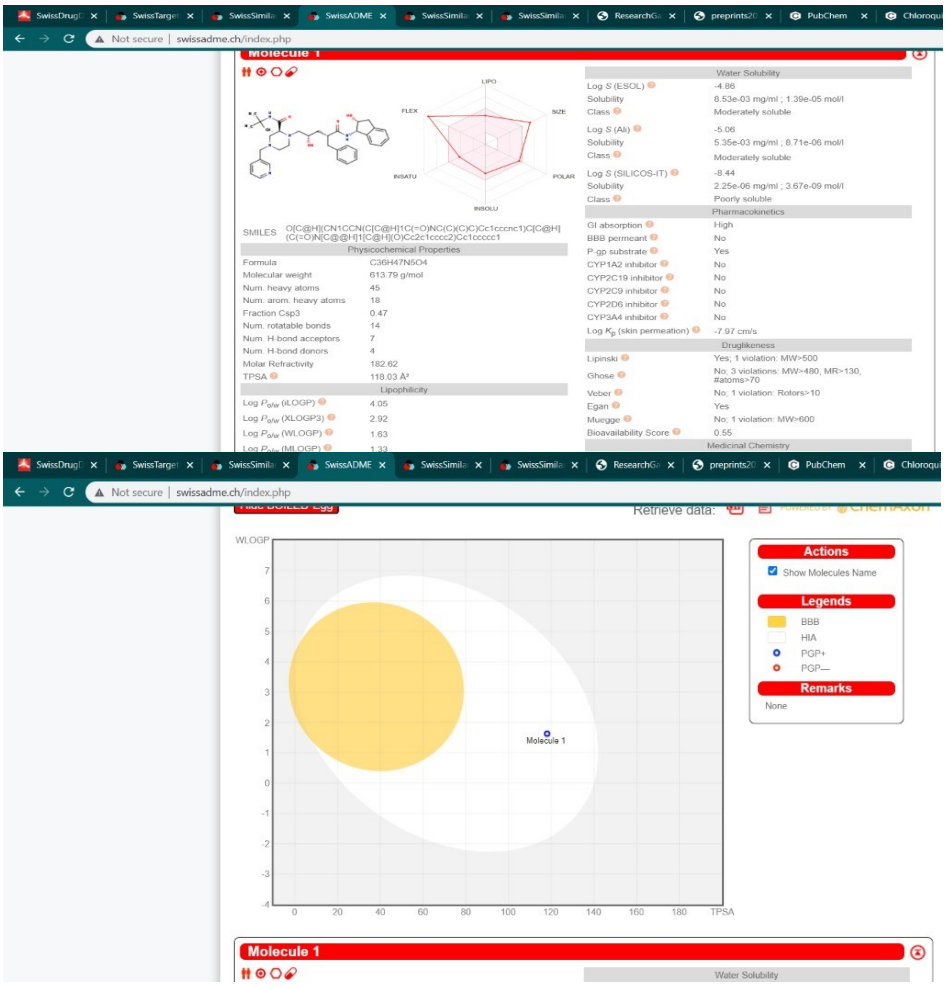

FIG. 5. Indinavir Boiled Structure

C. **Mizolastine**

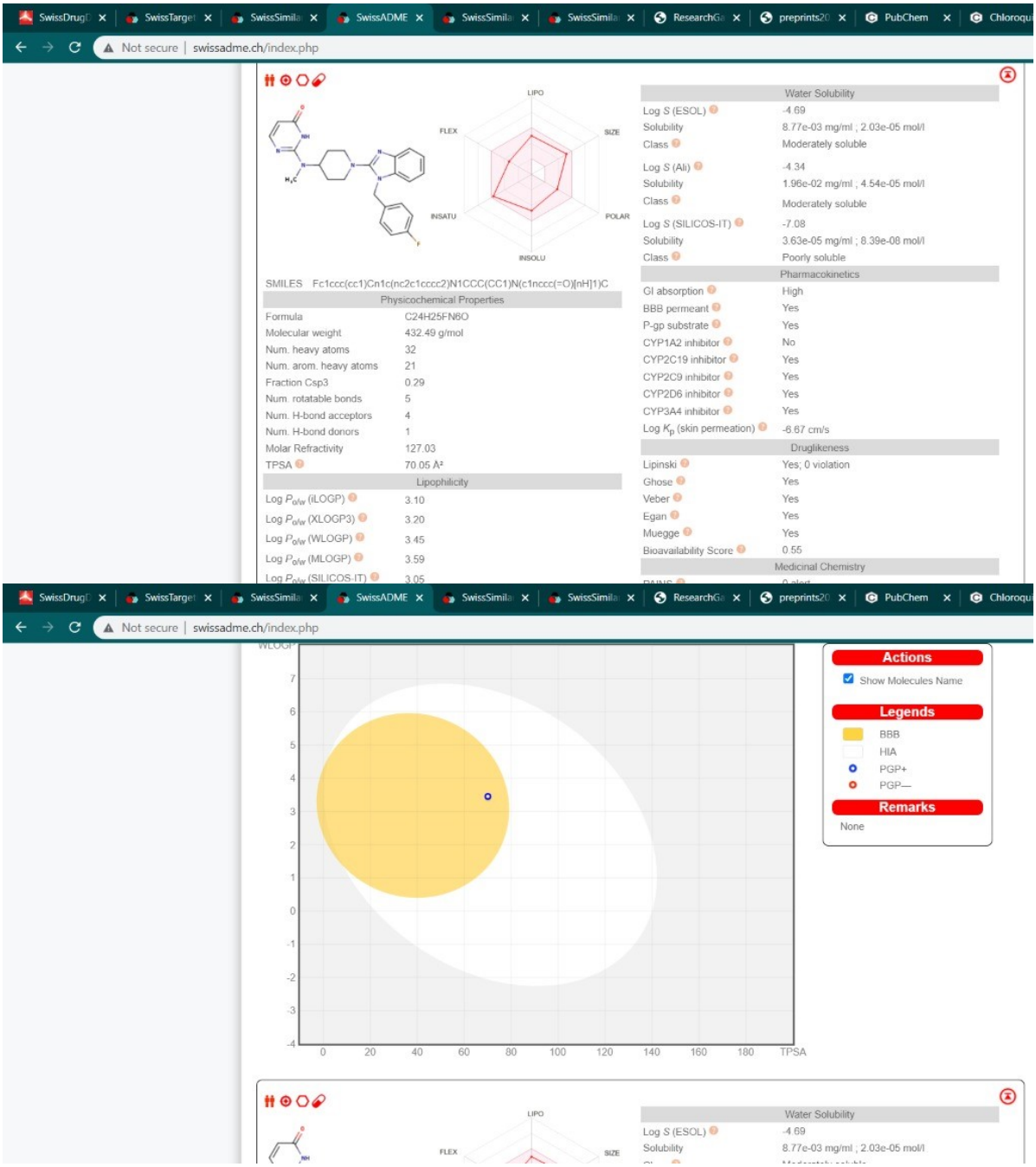

FIG. 6. Mizolastine Boiled Structure

D. Lymecycline

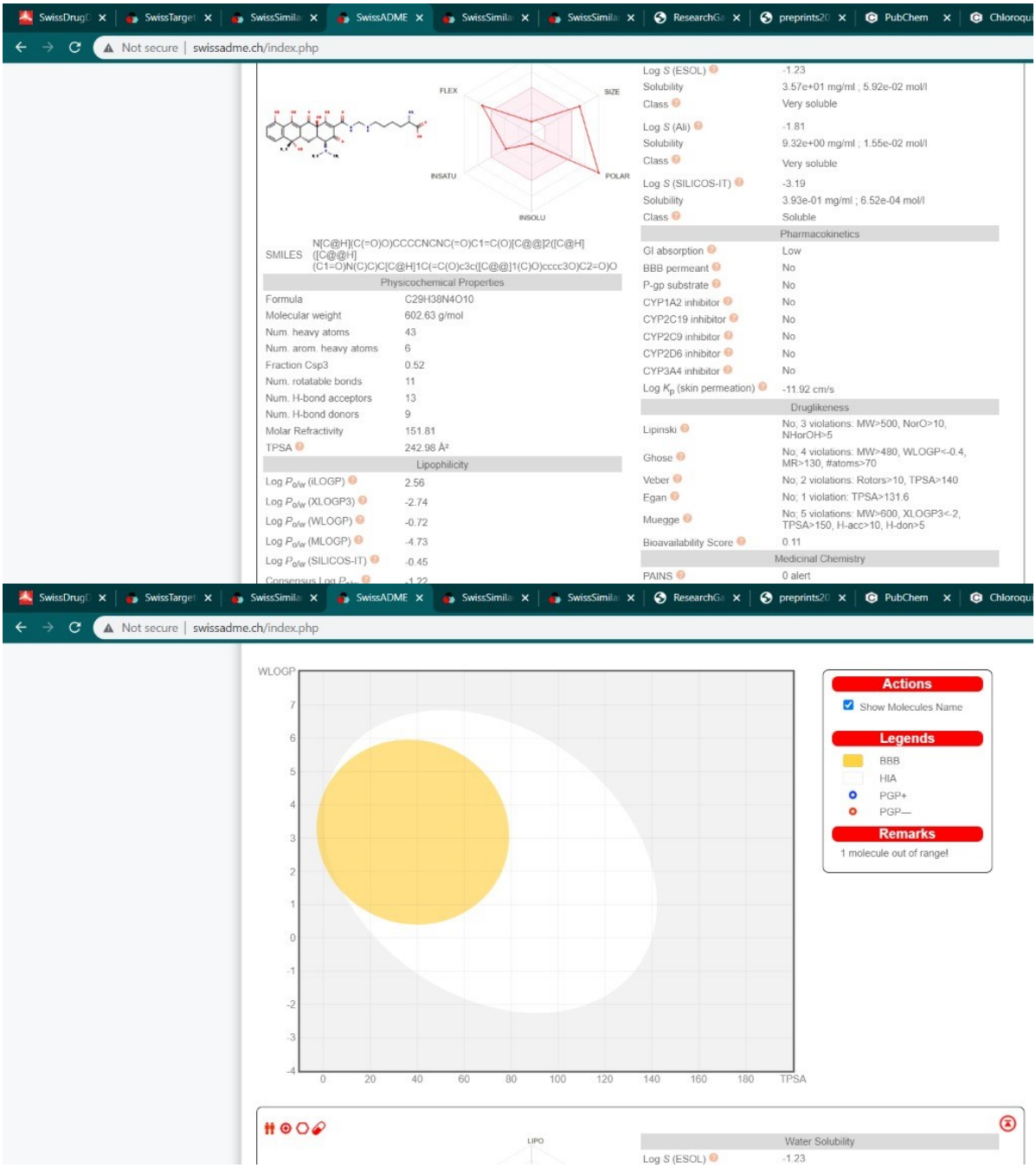

FIG. 7. Lymecycline Boiled Structure

It consists of large number of small molecules in its database, and we can access it by entering either the SMILES or structure code of the desired molecule or ligand.
We can further modify its properties based on our interest.

2.2.1 Boiled egg:

It evaluates gastrointestinal absorption and brain penetration. Nonblack shaded region tells us high chances for GI tract and turmeric shaded region indicates high chances for brain penetration.
To summary we can conclude all the properties in a table to understand in better form

Table: -1 Properties

Compound	Water solubility	Lipophicity	Gi absorption	Bbb permeability	Bioavailability score
indinavir	Poor solubility	2.78	high	no	0.55
chloroquine	Poor solubility	4.15	high	yes	0.55
mizolastine	Poor solubility	3.28	high	yes	0.55
lymecycline	soluble	-.122	low	no	0.11

Summary:

From above table we can understand chloroquine and mizolastine have 4interesting features such as high lipophicity, bioavailability score of 0.55, higher GI absorption. From the table we can see that lymecycline is more soluble than rest 3 compounds. With the Bioavailability score of 0.11. As Pglycoprotein plays an important role in bioavailability.

2.2.2 Binding pocket prediction:

It is a Web service that has been used to forecast the targets for bioactive small compounds in humans and other vertebrates since 2014, with a major upgrade in 2019. This

is important for understanding the molecular pathways underpinning a certain phenotypic or bioactivity, rationalizing probable positive or negative side effects, anticipating known compound off-targets and setting the way for therapeutic repurposing to produce predictions, a ligand-based method is utilised, which is based on similarities between a query molecule and the known ligands of a large known protein targets. A new algorithm, new data, and a revised Web interface were recently added to the application. Swiss Target Prediction is the only publicly available online tool that uses both 2D and 3D techniques to score chemical similarity.

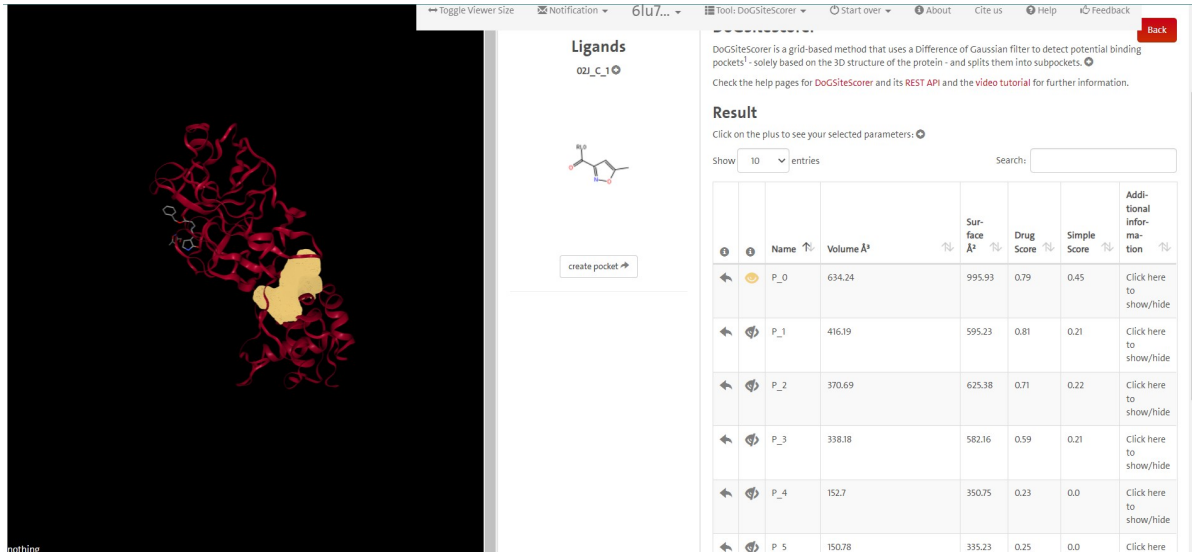

FIG. 8. Binding pocket Prediction - 1

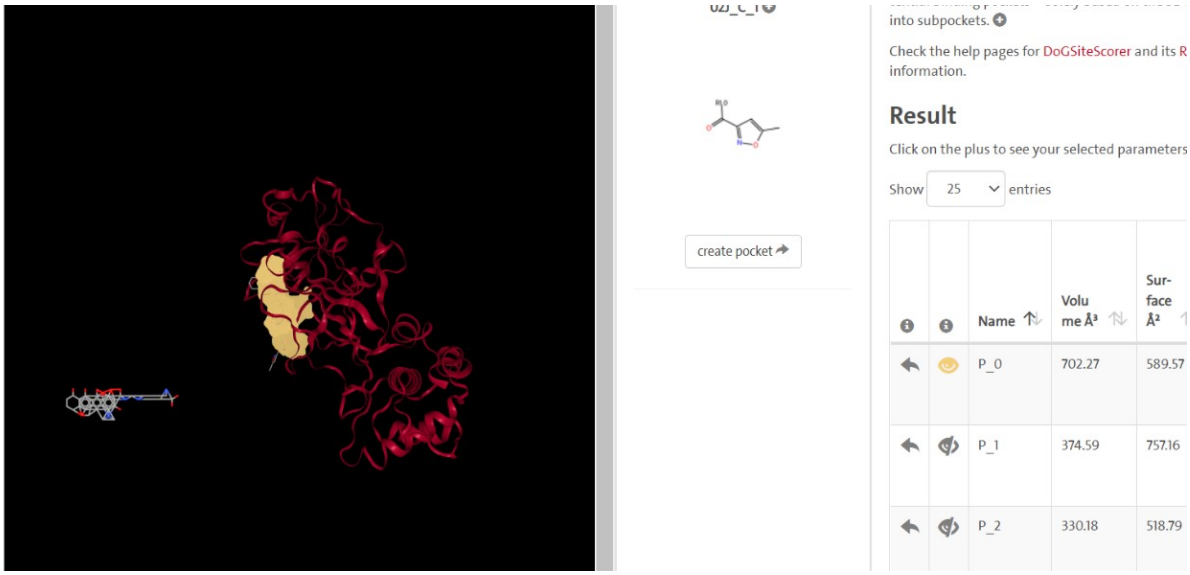

FIG. 9. Binding pocket Prediction - 2

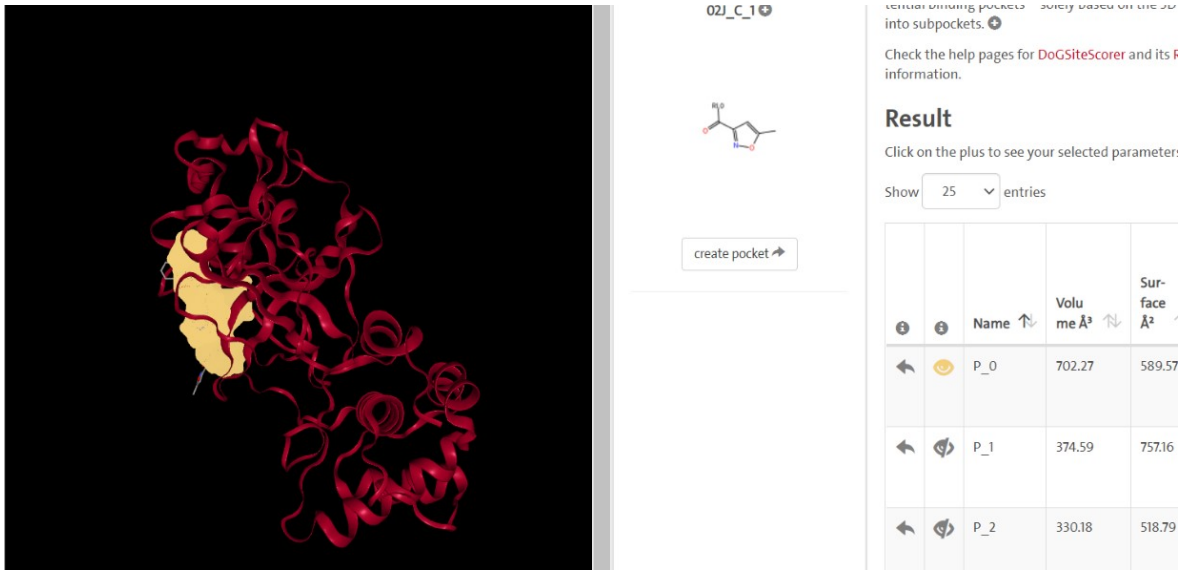

FIG. 10. Binding pocket Prediction - 3

Table: - 2. Volume, Surface Area, Drug Score

Structure	Pocket no.	Volume	Surface area	Drugs score
6lu7	0	634.24	995.93	0.79
	1	416.19	595.23	0.81
	2	370.69	625.38	0.71
6lu7+mizolastine	0	702.27	589.57	0.83
	1	374.59	757.16	0.74
	2	330.18	518.79	0.56
6lu7+lymecycline	0	702.27	589.57	0.83
	1	374.59	757.16	0.74
	2	330.18	518.79	0.56

CHAPTER 3

DOCKING

Swiss dock is a docking software where prediction of interaction between different species at molecular level is obtained which thereby passes path for a precise drug. Swiss dock provides software for protein engineering wherein we can edit structure and ligand to stabilize the target and increase its affinity

1. First, we required the structure of our target protein from PDB (protein data bank) PDB carries different characteristics like crystallography.
2. Next the computation is carried out from the secure side and the docking result are presented
3. Then there was a docking process that is we are doing in this software
4. Target selection: - a target pre-defined from PDB data base and uploaded
5. Ligand selection a ligand is selected from zinc database from which we can readily access compounds for virtual screening zinc database has some over 250 million compounds ready for docking.
6. Docking parameter:
    a. Very fast
    b. Fast
    c. Accurate
7. Very fast- a ligand having fewer rotatable bonds and it fits into binding vacancy and target. If target protein is large and if binding position area already assumed docking is restricted.

3.1. BLIND DOCKING

Blind docking was used with a Swiss Dock server in the accurate option with no mobility of the chain length of any amino of the protein to explore the chemical bonding

between numerous authorized drugs and COVID-19 major protease (Mpro). Furthermore, no binding pocket was created to avoid biassing docking toward this active site. PDB and MOL2 files used.

Swissdock gives best binding forms for ligand. favorable binding interactions for each pocket. All chemical clusters were stored in a "prediction file" output file. Computed binding free energy is given in the prediction file. The one with the lowest binding energy was chosen for further usage.

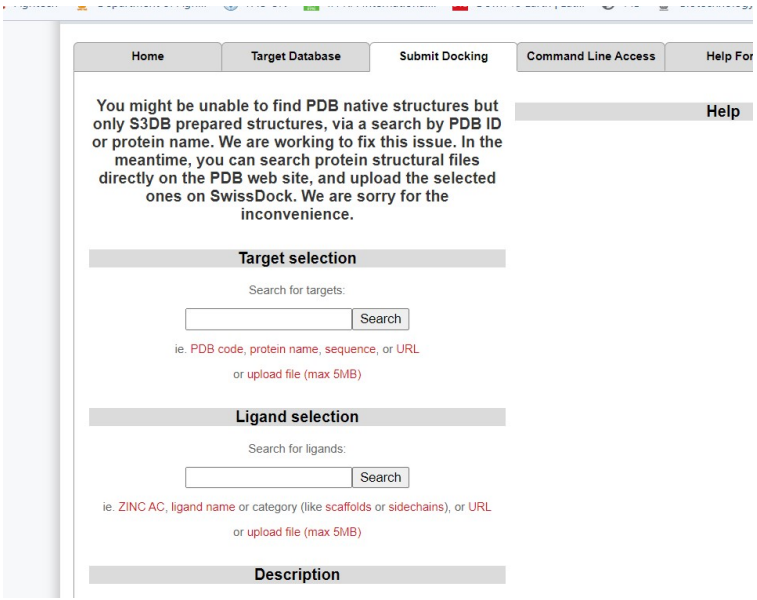

FIG. 11. Docking website

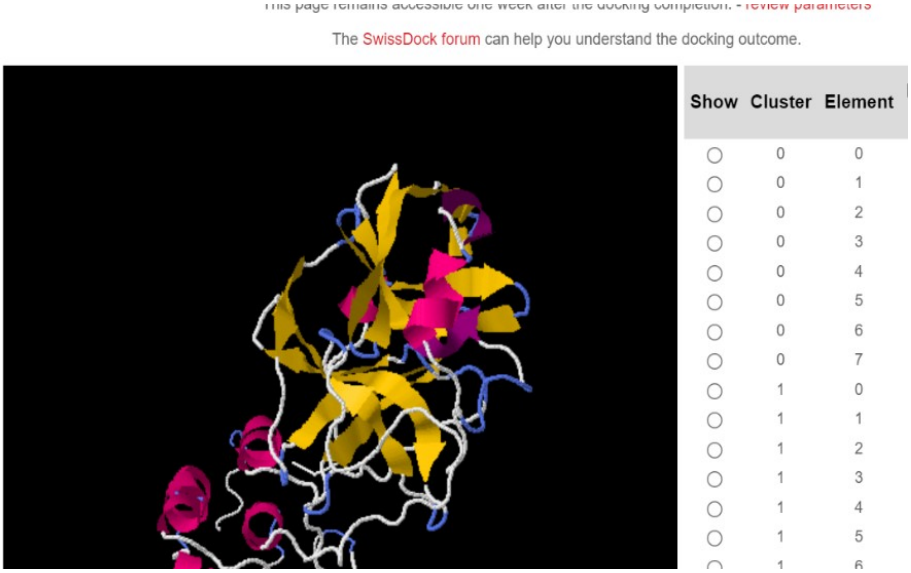

FIG. 12. Docking Results 3

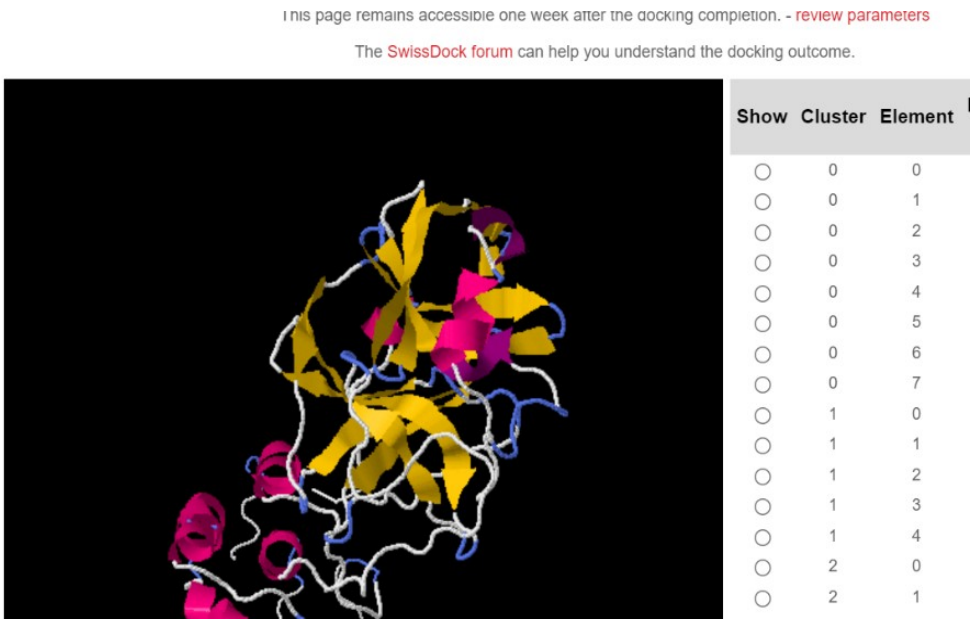

FIG. 13. BLIND DOCKING PROCEDURE

The study will employ two molecular docking approaches. SWISSDOCK was used for smaller molecule and virtual screening initially. The Blind Docking system was also utilized to forecast the lowest binding free energy in silico. Nine docking postures were constructed for each structure, and the values for the best docking images of each formation were used to rank them**.**

3.2. BINDING POCKET PREDICTION

Many CoV Mpro crystals have a well-defined binding site for N3. We also utilised the DoG Site Scorer online for estimate and characterise binding proteins in native Mpro and Mpro/inhibitor compounds generated through docking studies.

Based on a 3d structure, DoGSiteScorer is able to tell the binding pocket. As global properties, the expected (sub)pockets' size, structure, and chemical features are estimated. To rank them, the drug's ability, size, and surface area score are employed.

The gray area represents inaccessible sites which cannot be utilized for inhibition. Here different colors have different properties and values which are kept in considerations before virtual docking.

Below we can see how different color have different values of pocket rank, pocket score, etc.

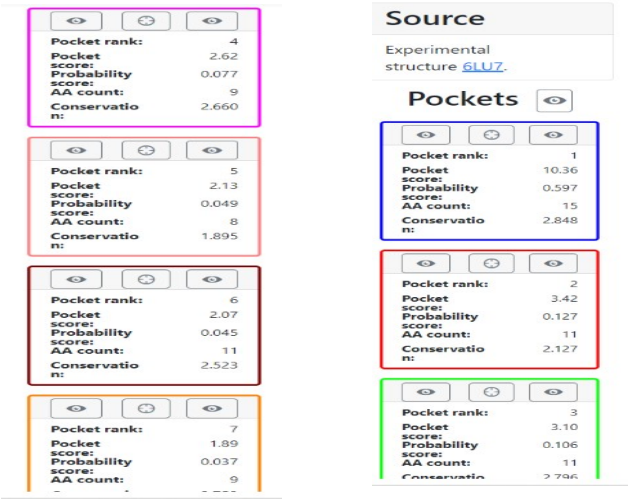

FIG.14. POCKET RANK AND POCKET SCORE

3.3. PHARMOKINETICS PROPERTIES

The two drugs taken into considerations Mizolastine and Chloroquine both have greater lipophilicity, a bioavailability of 0.56, and increased GI absorption, after analysis. The N3 compounds absorption is poor and the bioavailability score is of around 0.12. When compared to Chloroquine, toxicity data analysis revealed that Lymecycline and Mizolastine are safe to use.

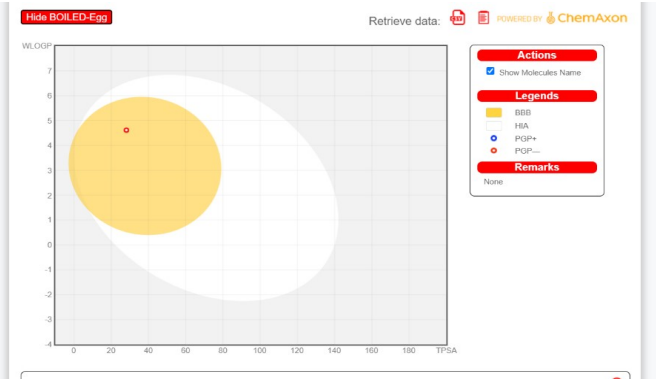

FIG.15. BOILED EGG DIAGRAM

CHAPTER 4

CONCLUSION

Using swiss drug design as a software for different purposes gives efficient output. We had used:

A. Swiss docking
B. Swiss adme
C. Pocket prediction
D. DoGSiteScorer

An aftermath compilation of all the above software renders the best and effective drug based on many different properties but we were only interested in binding energy. And the literature suggests that one with the least binding free energy was the best amongst the cluster of drugs initially taken.