TO ESTIMATE HIGH-AFFINITY LIGANDS AS AN INHIBITORS OFSARS-CoV-2 VIRAL PROTEIN BY VIRTUAL SCREENING TOOL

YASH RANGA[1], HARSHIT KANCHAV[2]*, Dr. ANITA SINGH[3], Dr. AMITA JOSHI RANA[4]

1. M.Pharm., Department of Pharmaceutical Sciences, Sir J.C. Bose Technical Department, Kumaun University, Bhimtal, Nanital, Uttarakhand, India-263136
2. Assitant Professor, Lloyd Institute of Management and Technology, Plot no.-11, Knowledge Park-II,Greater Noida, Uttar Pradesh, India-201306
3. Associate Professor, Department of Pharmaceutical Sciences, Sir J.C. Bose Technical Department, Kumaun University, Bhimtal, Nanital, Uttarakhand, India-263136
4. Assistant Professor, Department of Pharmaceutical Sciences, Sir J.C. Bose Technical Department, Kumaun University, Bhimtal, Nanital, Uttarakhand, India-263136

****Corresponding Author:Harshit Kanchav**
boxofharshit@gmail.com

Abstract: It was found that the drug discovery and development is a very time consuming and costly process. For reducing the time and cost Cadd is come. In thiswe have to discuss about the high-affinity ligands which inhibits the SARS-CoV-2. Some compounds docking score are good, but these are not considered because they cannot follow the Lipinski rule. Virtual screening involves the selection of specific drug candidates from the large library of various of chemical structures using the computational methods. When detecting the compounds with comparable shapes, ROCS uses a shapes-based position. In this study we must discuss what are the major cause for SARS-Cov-2 and how it can be resolve by using virtual screening.

Keywords: COVID-19, ACE2, SARS-COV-2, Molecular docking.

INTRODUCTION

The novel coronavirus is the 7th human coronavirus which is identified in Wuhan, China in December 2019. There are 4,806,300 people are infected in which 318,600 deaths by the virus spreading worldwide at 20 May 2020. SARS-CoV-2, SARS-CoV, and MERS-CoV are three human coronaviruses that cause pneumonia and have mortality rates of 2.9%, 9.6%, and 36%, respectively. NL63, HKU1, OC43 and 229E there are four other human coronavirus having mild symptoms.[1] The respiratory illness which is caused by the noval coronavirus is called as COVID-19 by the WHO. It contains large RNA virus which is positive and single-stranded can infect the humans and also very large range of the animals. According to the recent studies of COVID-19

which indicates that the patients≥60 years of age are at the higher risk as compared to the children, although it shows mild symptoms or asymptomatic infection. The receptor ACE-2 serves as a receptor for entering COVID-19 to infect lung alveolar epithelial cells. The new coronavirus has four subfamilies: beta-, delta-, alpha-, and gamma-coronavirus. Gamma and the delta coronavirus are derived from birds and pigs, while beta and alpha were derived from mammals, primarily bats. [2]

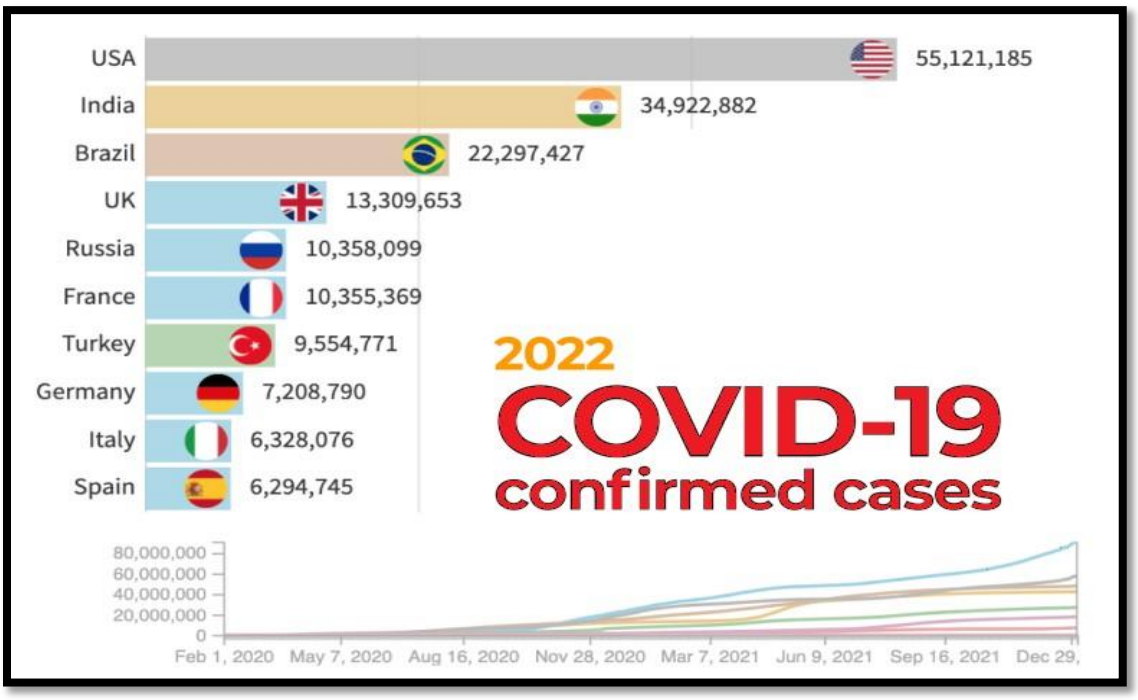


Figure 1: SARS-CoV-2 cases which are confirmed worldwide as of the year2022.[3]

Many COVID-19 carriers experience neurological problems and also mental health problems. Cardiovascular system harm from SARS-CoV-2, including chronic and acute cardiac damage is possible. There are 12% patients are found in China having acute myocardial injury with COVID-19. The DAD (diffuse alveolar damage), a term used in histology to describe specific changes that occur in the structure of the lungs throughout accidents or diseases, was found in the post-mortem reports of patients who died as a result of SARS-CoV-2.

EXPERIMENTAL

Protein preparation

All the outcome shared with colleague or if used externally there is requirement of expert, since

the project table organised all the mediatory structures. Preparation process is start by the user at any stage or at any time. All the non-essential molecules are removed, except the essential water molecules and the heteroatoms. For lower the size of proteins OPLS3 forcefield were used. Proteins active site co-crystal ligand (1R42 and 6Y2F) were used by the scientists for the creation

of the grid, after docking in extreme precision mode with its co-crystal ligand (XP), the protein's RMSD must be determined. The Schrodinger slingshot is anticipated to be available in time for Euro 2019e. The protein preparation wizard tool is a helpful tool for chemical processes that depend on accurate protein models and for creating a solid starting point for activities involving structure-based drug development. Protein preparation wizard is used manually which can save the time and effort.

Receptor grid preparation

Grids are utilised for the GLIDE docking approach to help in protein docking. To build the grid box there is a use of active site size and the centroid of the co-crystal ligand. The active pocket is enclosed and all the adjacent amino acid are covers by the grid. The grid box consists of two boxes: the grid box and the midway box, both of which allow the ligand centre to move about freely. Because of this in the grid-lined box there is only changes in the ligand when using the ligand selection option. Construction of the grid box is accomplished by selecting the centroid of the residue and leaving all other GUI site tab settings at their default positions due to the absence of crystal ligand.

Ligand preparation

The chemical database that the docking study was referring to produced hits through virtual screening for the ligands used. Built-in ligands and OPLS3e force field decrease the amount of energy which are required to observing the calculations in this programme (Schrodinger,2019). In the docking studies, addition of hydrogen to ligands, minimization simplifies bond ordering arrangement, conversion of 3D structures from 2D structures are take place. The output file of the programme benefits the docking study. The program's output file with the best potential ligand conformations.

Molecular docking study

After removing any solvent molecules and minute molecular ligands from the protein, docking is

initiated. The physiological circumstances and docking are not coupled when this procedure is

performed. The Intel i5 11th generation CPU performs compound docking tests using the Schrodinger Glide module. The table displays the chemical's molecular weight. In the RCSB protein structure database search, the protein was discovered along with the structure. When enhancing the lead compounds, it is important to comprehend how medications interact with their target at the atomic level and create protein-ligand complex structures.

Prediction of ADME

Swiss ADME predicted result are shown below in the table, which might be freely accessed at http://www.swissadme.ch. It is simple to use for the people who are not expert in CADD and simply analyse data. The advantages of the Swiss ADME are the ability to display, share, save data from the individual molecules and the interactive graphs, the other free web-based ADME prediction programmes don't include any of these (admetSAR15, for instance and pk-CSM14). Swiss ADME have more advantages in which it has unique access to highly effective procedures. Finally, the Swiss Drug Design system is connected to the Swiss ADME. The characteristics of the molecules are provided in this section. Once the computations are done, it runs one molecule at a time.

Result and Discussion

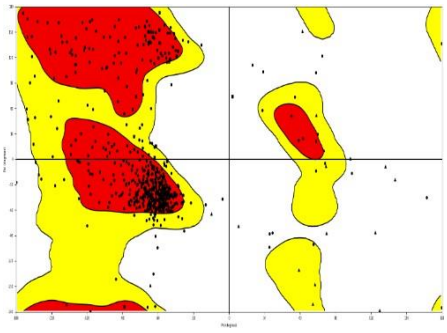
Preparation of protein: -

Making the reduced 3D molecule structures by ionising the 2D structures with Lig. Prep., 90,701 and converting them to 3D structures. The docking of crystal formations is allowed in these energy-saving 3D structures. The protein preparation wizard tool was used to generate the viral ACE 2 and Protease by optimising the H-bond network and reducing geometric complexity (1R42 and 6Y2F). By the addition of the missing hydrogens and precise ionisation states which improved the force field treatment and charge assignment. Proteins and ligands interact strongly (Mol. Dock scores: -9.451 for PDB ID-1R42 and -7.214 for PDB ID-6Y2F), and hydroxychloroquine demonstrated a high affinity for binding (Mol Dock score-5.329 for PDB ID-1R42 and -4.459 for PDB ID-6Y2F). The following figures depict the 3D interaction of the ligand with the binding site. There are slight variances in the interacting amino acids because binding affinities of all the drugs

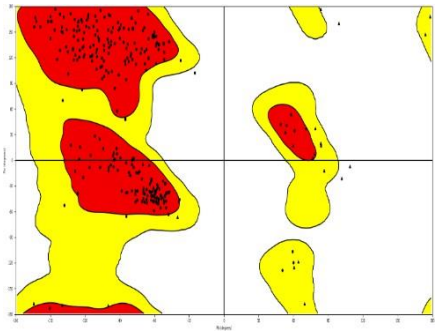
are the same when using the open protein form.

Receptor grid generation

Docking results are displayed in Table 1 below. The produced proteins' Ramachandran plot is displayed in the figures below. The EB value is increased by the inverse relationship between EB and Ki. After the administration of medicines, affinity to bind to the receptors in which hydrogen bonding play a role. This demonstrates that the strength of hydrogen bonding is correlated with the strong affinity for protein-ligand binding.

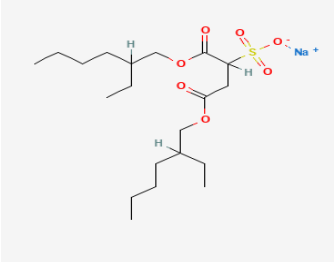


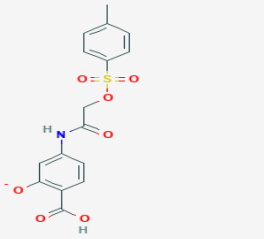
PDB ID: 1R42

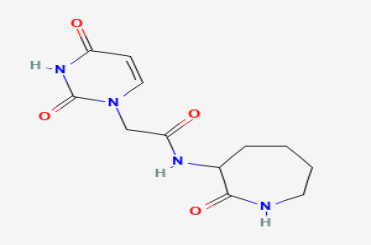
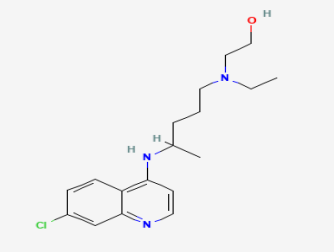
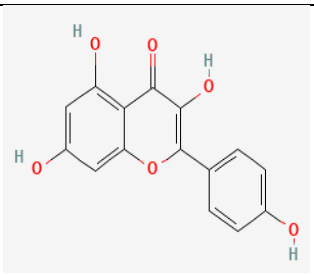
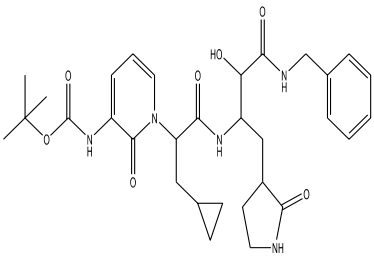
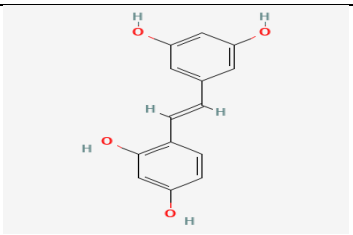


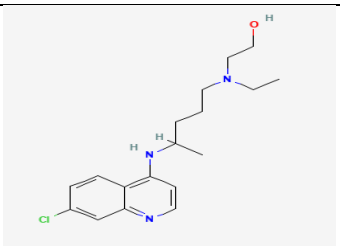
PDB ID:6Y2F

Table 1: Docking score of top-most compounds

S. No	ID of compound	Structure of compound	Compound IUPAC Name	Docking Score	Gliding score
For PDB ID-1R42					
1.	S4588 Docusate sodium.cdx		Sodium,1,4-bis(2-ethylhexoxy)-1,4-dioxobutane-2-sulfonate	-9.451	-9.451

2.	S31-201.cdx		2-hydroxy-4-(2-(tosyloxy)acetamido)benzoate	-9.156	-9.156

3.	maegz:158		2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N-(2-oxoazepan-3-yl)acetamide	-8.625	-8.625
	Standard drug Hydroxychloroquine		(RS)-2-[{4-[(7-chloroquinolin-4-yl) amino] pentyl} (ethyl)amino] ethanol	-5.329	-5.329
For PDB ID-6Y2F					
1.	Kaempferol.cdx		2,3-dihydro 3,5,7trihydroxy-2- (-4-hydroxyphenyl) chromen-4-one	-7.214	-7.214
2.	maegz:274		tert-butyl (1-(1-((4-(benzylamino)-3-hydroxy-4-oxo-1-(2-oxopyrrolidin-3-yl)butan-2-yl)amino)-3-cyclopropyl-1-oxopropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)carbamate	-6.870	-6.870
3.	S4739 oxyresveratrol.cdx		4-[(E)-2-(3,5-dihydroxyphenyl) ethenyl] benzene-1,3-diol	-6.807	-6.807

	Standard drug Hydroxychloroquine		(RS)-2-[{4-[(7-chloroquinolin-4-yl) amino] pentyl} (ethyl)amino] ethanol	-4.459	-4.459

Estimation Profile for ligands

LigPlot was employed to produce the 2D plot of the ligand-S-RBD molecular interaction. Afterthe docking of proteins docking poses of each molecule are estimated. It was found that the SARS-CoV-2 S-RBD residues S4588 Docusate sodium, s31-201, maegz:158, Kaempferol.cdx, maegz:274 and S4739 oxyresveratrol interact with the ligands after the docking calculations.

Table 2: Physicochemical properties of top-most compounds

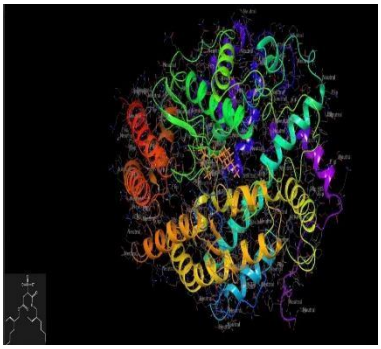
S. No.	**ID of compound**	**Mol.wt. of compound**	**HBD of compound**	**HBA of compound**	**Molar refractivity of compound**	**TPSA**	**Water SolubilityClass**
For PDB ID-1R42							
1	S4588 Docusate Sodium.cdx	444.558	0	7	109.51	118.18 Å²	Moderate lysoluble
2	S31-201.cdx	365.357	2	8	69.41	108.95 Å²	Soluble
3	maegz:158	280.283	2	8	59.10	86.10 Å²	Soluble
For PDB ID-6Y2F							
1	Kaempferol.cdx	286.236	3	4	76.01	111.13 Å²	Soluble
2	maegz:274	286.361	1	4	124.84	99.51 Å²	Moderately soluble

3	S4739 oxyresveratrol.cdx	244.243	4	4	69.90	80.92 Å^2	Soluble

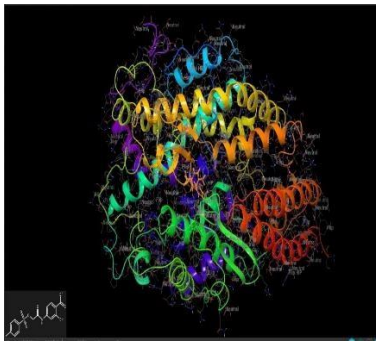
Table 3: Pharmacokinetic profile of top-most compounds

S. NO.	ID of compound	Log p value of compound	Log Kp (Skin permeability)	GI absorption of compound	BBB permeant of compound
For PDB ID-1R42					
1.	S4588 Docusate Sodium.cdx	2.11	-5.36cm/s	Low	No
2.	S31-201.cdx	0.99	-6.31cm/s	High	No
3.	maegz:158	-1.57	-7.16cm/s	Low	No
For PDB ID-6Y2F					
1.	Kaempferol.cdx	1.58	-6.70cm/s	High	Low
2.	maegz:274	0.39	-8.23cm/s	Low	No
3.	S4739oxyresveratrol.cdx	2.08	-5.82cm/s	High	Low

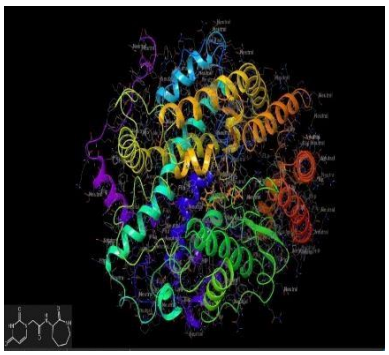
Docking images of top-most compounds for PDB ID-1R42



S4588 Docusate sodium.cdx

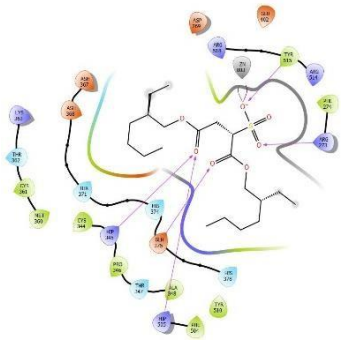


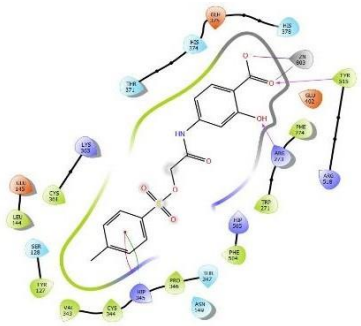
S31-201.cdx

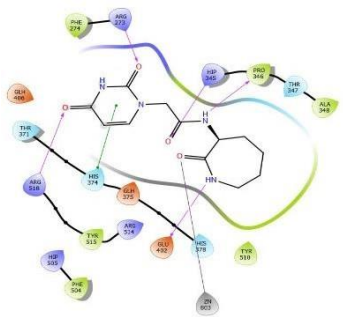


maegz:158

Ligand interaction of top-most compounds for PDB ID-1R42

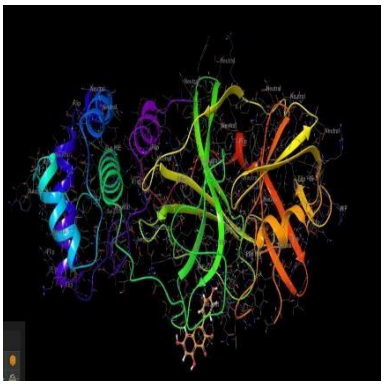




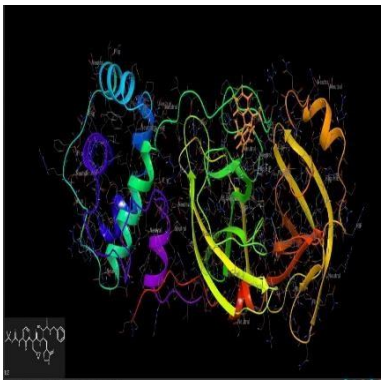


S4588 Docusate Sodium.cdx **S31-201.cdx** **maegz: 158**

Docking images of top-most compounds for PDB ID-6Y2F



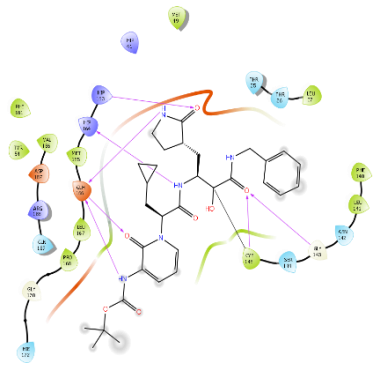
Kaempferol.cdx
oxyresveratrol.cdx



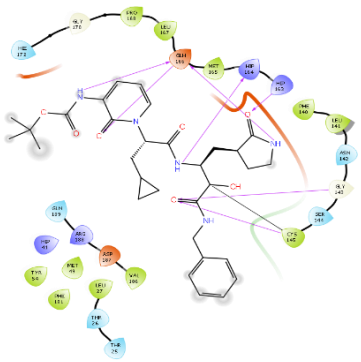
maegz:274

S4789

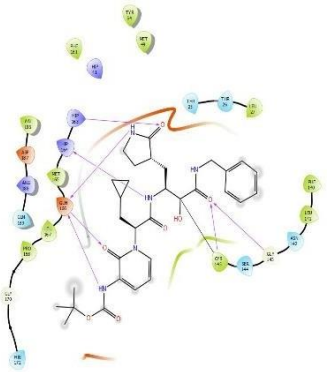
Ligand interaction of top-most compounds for PDB ID-6Y2F



Kaempferol.cdx
oxyresveratrol.cdx



maegz:274



S473

Conclusion: -

For creating the antiviral therapies to fight and cure the COVID-19 researchers find out the pathogenesis and host range brought on by virus receptors will aid scientists in developing antiviral medications. For noval coronavirus, there is no antiviral medication. COVID-19 infection is the

worldwide problem which is recognised by WHO. Molecular docking and structure-based drug design are utilised to search the novel bioactive compounds that are described below. Concerning the scoring functions' precision, which is essentially an approximation controlled by quantum

physics, there are issues that arise. Small molecule ligands' binding modalities to protein binding sites are primarily predicted by docking methods. In agreement with the findings of antiviral library screening, the host cell receptor ACE2 protein and the SARS-S-RBD CoV-2s protein interact with the chosen ligands in molecular docking studies. A crucial stage in the replication cycle is the connection between the viral protein and its cell membrane protein, in which the spike(S) protein interacts with the ACE2 receptor. Some compounds docking score are good but these are not considered and which are not mentioned in the table because they cannot follow the Lipinski rule.

There are some prominent compounds S4588 Docusate sodium.cdx, S31-201.cdx, maegz:158 for protein PDB ID-1R42 and Kaempferol.cdx, maegz:274, S4739 oxyresveratrol.cdx for protein PDB ID-6Y2F. It can be concluded that the chosen compounds show promise and can be exploited to develop powerful anti-SARS-CoV-2 medications.

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