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Molecular Docking and the Pharmacokinetic Properties of the Anti-Viral Compounds Towards SARS-CoV- An In-silico Approach

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ABSTRACT

The main aim of this study is to determine the bioactive compounds which have drug-like properties and has the potential to combat the spike-glycoprotein of SARS-CoV-2. The 6LXT protein of covid-19 was chosen from the protein data bank as a target protein. The compounds which are potentially capable to bind with the target were picked from the PubChem database and docked using the tool Autodock 4.2. Molecular docking of the molecules was done with the best conformations of the ligands and grid size was selected according to the hit compounds' interaction with the target protein. The ligand binding sites with the target molecules were predicted using MetaPocket 2.0. The docking Score of 50 compounds wascarried out and also toxicity studies were carried out. The compounds selected were calculated to identify the best conformations having drug-likeness properties. The top 10 compounds were chosen for the structure-activity relationship based on their binding interactions with the protein and ligand. The ligands then underwent the pharmacokinetic analysis followed by Lipinski's and all the results were finalized and categorized. ManzamineA, Imatinib, and basotinib were elected as the peak compounds with the binding energy -9.01kcal/mol, -8.71kcal/mol, and -8.01kcal/mol.

Key words: *Lead compound, Molecular docking, Covid-19, Pharmacokinetic properties*

INTRODUCTION

The outbreak of Covid-19 has affected the entire world and it's been considered the prominent human pathogen globally. There is a search for new drugs to control the multiplication of this novel virus that is causing severe respiratory infections. The existing drugs are considered a suitable option for the search for potent drugs for the virus to get the cure for the disease. Sars-Cov-2 is been considered one of the most severe mortality infections because of its wide range of severity and globally many people have been dead because of this infection [1, 2]. The Covid-19 virus contains RNA viruses with a size of around 26-30 kilobases and it causes respiratory illness in humans and animals. The virus belongs to the family of four genera named alpha, beta, gamma, omicron, and delta viruses. Mostly all the viruses families have been affected the various parts of the world. The infection has spread from the lungs to the central nervous system making the whole body in a worse state. The sequences of the SARS-CoV family have been studied and found that the beta coronaviruses have been spread among mammals, bats, and rodents with sustained genetic evolutionary features. The Covid-19 virus contains glycosylated spike protein, membrane protein, nucleocapsid protein A 1255 aminoacid type I membrane spike glycoprotein [3-5]. The spike-like glycoproteinin SARS is the protein that is found in the viral membrane to construct the spike structure which is found in all SARS-CoVfamilies [6, 7]. This paper outlines the use of In-

silico structure-based molecular docking and simulation approaches to study the binding interactions of the potential antiviral compounds.

MATERIALS AND METHODS

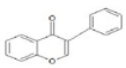
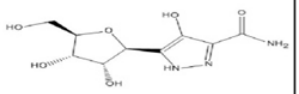
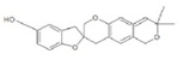
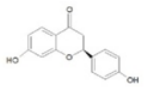
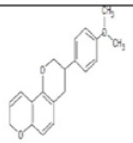
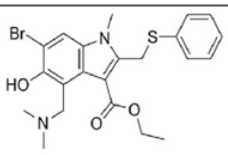
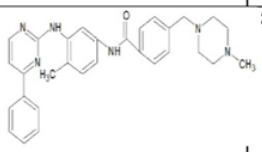
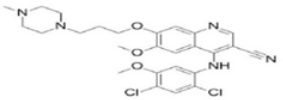
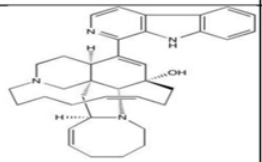
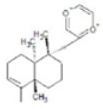
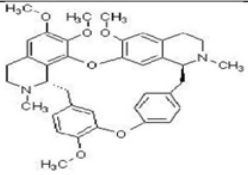
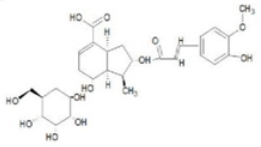
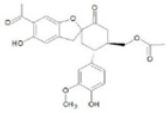
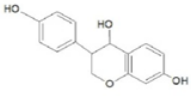
The online tools and software used for the study were MGM-Autodock software, Python 3.8, Discovery studio image processor, and ADME Toxicity Estimation software tool [8, 9].

System information

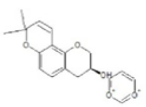
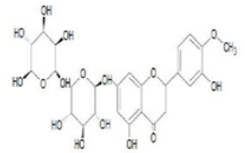
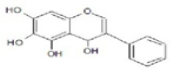
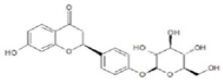
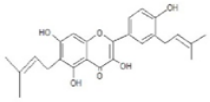
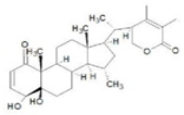
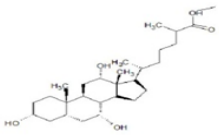
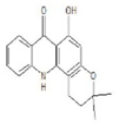
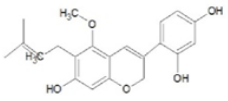
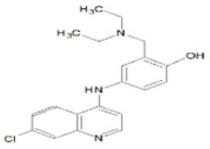
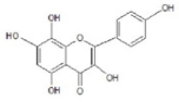
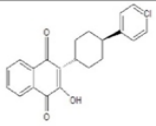
For the in-silico analysis, the following system with the configuration has been used for the study. The processor used for the entire study is an Intel core i3-7100U CPU-2.40GHz, 4 GB RAM,32-bit windows 7 operating system. The terms and agreement have been followed as prescribed in the software manual.

Ligand preparation

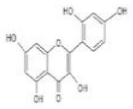
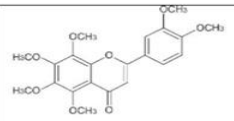
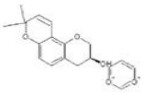
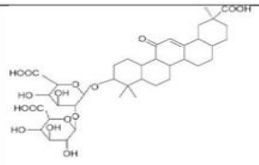
Around 30 natural antiviral compounds have been studied through various literature and the compounds have been retrieved from the PubChem database. The downloaded molecules were converted into PDBQT canonical smiles format using the Autodock software tool. Moreover, the molecules were converted into PDB files for docking studies. The compounds selected for the study have been represented in **Figures 1a-1c** [10-12].

Ligands	Structures	Ligands	Structures
1.Isoflavones		2. Isoliquirtin	
3.Shinpterocarpin		4. Liquirtigenin	
5. 3'-Hydroxy-4'Glabridin		6. Arbidiol	
7. Imatinib		8. Bosutinib	
9. Manzamine A		10. Avarol	
11. Tetrandrine		12. Khanaoside B	
13. Propolis		14. Diadzein	

a)

15. Glabridin		16. Diosmin	
17. Baicalein		18. Liquirtin	
19. Glyasperin A		20.Deoxywithaferin A	
21. Ethyl cholate		22. Acronine	
23. Dehydroglyas-perin C		24. Amodiaquone	
25. Herbacetin		26. Atovaquone	

b)

27. Morin		28. Nobiletin	
29.Glabridin		30.Reference ligand	

c)

Figure 1. a) Details of the molecular structures of the 30 compounds taken for the study [8, 9]. b) Details of the molecular structures of the 30 compounds taken for the study [13, 14]. c) Details of the molecular structures of the 30 compounds taken for the study [15-17]

Protein preparation

The PDB ID 6LXT has been retrieved from the Protein database and the water molecules present in the protein have been removed. As water molecules play a vital role they have been removed for efficient docking purposes. The hydrogen atoms were added to the protein molecule and the protein has been prepared using the Protein preparation wizard. Missing atoms and loops, hydrogen atoms, and assigning bond orders have been done using the preparation tool wizard which is available in the Autodock software tool [18]. The retrieved two-dimensional structure has been depicted in **Figure 2**.

Determining the active site

The active site of the protein plays an important role in the activity of the protein. Targeting the active site will help develop more lead molecules toward the infections. The amino acids surrounding the active site have been

determined using the Metapocket-Online server tool. Based on the active site determination, a grid box is generated for the effective docking of the ligands. The grid size for this protein molecule is X=72, Y=58 & Z=126. The other parameters in the tool were kept default. The grid center was found to be -0.637, -12.021 & -44.463. GPF file format is used to save the grid file. The protein binding pocket which is an active site is mainly for its specificity. The binding site provides flexible and rigid interaction with the ligands so that they can easily accommodate the ligands. The mobility of protein is also determined using the binding pockets.

Docking studies using Autodock 4.2.

Structure-based drug designing is been adopted for this entire study [10]. The compound retrieved from the PubChem database has been used for the docking study. The selected thirty compounds were docked into the active site of the protein using the Autodock tool software available in the package. The reference ligand was docked initially and then the thirty compounds were docked to the active site and the docking scores have been validated using the hydrogen bonding interactions.

Visualization using discovery studio

The docked compounds with the active site of the protein have been visualized using an online tool Discovery studio and Pymol 2.3. Inorder to visualize the ligand interaction diagram Ligplot +v.2.2 is used to study the two-dimensional interaction. Both softwareshave been used to identify the binding pattern of ligands and the protein to study the structure-activity relationship of the compounds with the protein.

Pharmacological properties and lipinski's rule of five

Absorption, Distribution, Metabolism, and excretion of drug molecules are the essential pharmacological aspect thatneeds to be determined. This can predict by using ADmetSAR (http:/lmmd.ecust.edu.cn/admetsar1/). This property is mainly estimated to evaluate the crucial interactions with the ligand and the target non-ligand molecules. These properties can predict the pharmacological activities based on which we can analyze in-vitro whether the ligand can be developed into a drug-like molecule. Lipinski's rule of five mainly states the properties of the drug including molecular weight, Hydrogen bond donors and acceptors, solubility, and Molar Refractive index [19, 20].

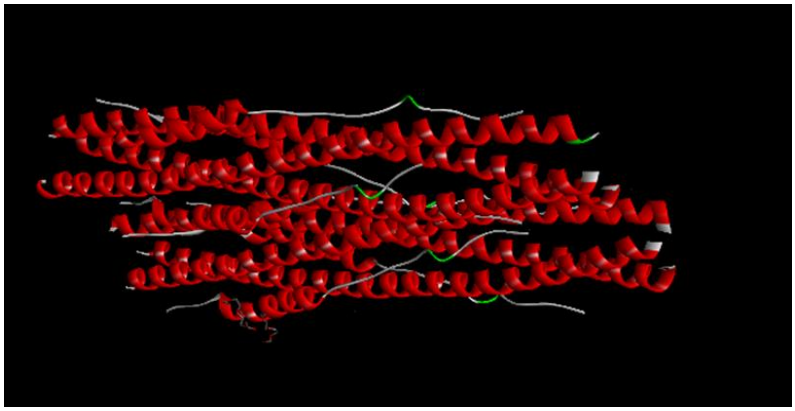


Figure 2. Three-Dimensional structure of Spike Glycoprotein (PDB ID:6LXT)

RESULTS AND DISCUSSION

The Docking results of the compounds revealed that the compounds showed good interaction with the protein 6LXT. The reference has well interacted with the active site of the protein and the docking score is found to be -6.3 kcal/mol. The top five compounds possessed good binding energy and the structure-activity relationship of the five compounds were studied. The compounds are Manzamine A, Imatinib, Deoxywithaferin A, Atovaquone, and Bosutinib [14, 21]. The docking scores of all the compounds have been tabulated in **Table 1**.

Table 1. The Docking Score of the compounds selected for the study

S.NO.	COMPOUNDS	DOCKING SCORE (Kcal/mol)
1.	Manzamine A	-9.06
2.	Imatinib	-8.71

3.	Deoxywithaferin A	-7.76
4.	Atovaquone	-7.06
5.	Bosutinib	-7.01
6.	Tetrandrine	-6.83
7.	Shinpterocarpin	-6.68
8.	3'hydroxy-4'methoxyglabridin	-6.47
9.	Glabridin	-6.47
10.	Ethyl Cholate	-6.41
11.	Raloxifene	-6.41
12.	Arabidiol	-6.23
13.	Pectolinarin	-6.14
14.	Acronine	-6.05
15.	Glyasperin A	-6.04
16.	Avarol	-6.04
17.	Liquirtin	-5.81
18.	isoliquirtin	-5.76
19.	propolis	-5.68
20.	Liquirtigenin	-5.52
21.	Morin	-5.56
22.	Dehydroglyasperin C	-5.49
23.	Herbacetin	-5.44
24.	Khainoside B	-5.32
25.	Amodiaquine	-5.29
26.	Diosmin	-5.13
27.	Baicalein	-5.11
28.	Isoflavone	-5
29.	Daidzein	-4.89
30.	GlycyrrhizicAcid	-4.3

Binding analysis and ligand interaction of manzamine A

The binding interaction of the compound Manzamine A reveals that the compound has well occupied into non-polar interactions. The compound has good hydrogen bonding interaction with Asn1194, Asp1199, Leu1197, and Ile1198. The compound revealed abinding score of-9.06kcal/mol. The ligand interaction and the 3-Dimensional representation of the compound Manzamine A havedepicted in **Figure 3**.

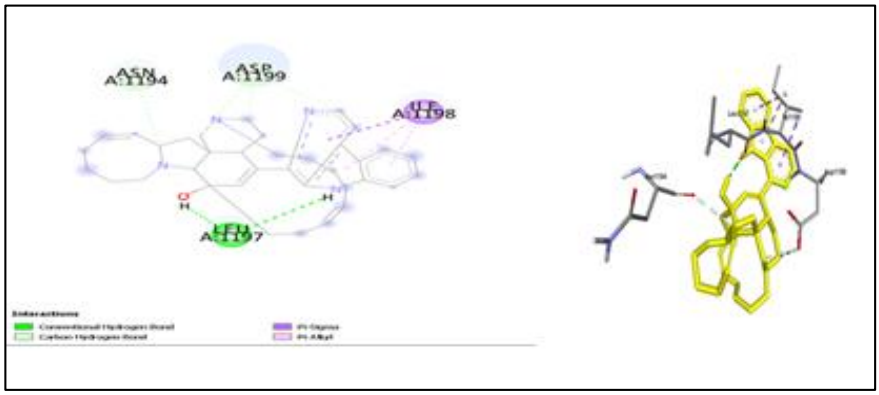


Figure 3. 2D and 3D Interactions of ManzamineA with 6lxt spike glycoprotein.

Binding analysis and ligand interaction of Imatinib

The binding interaction of the compound Imatinib reveals that the compound is well occupied with the Non-Polar Aminoacids Tyr917 and Ile1198. The important aminoacids which facilitate good docking scores are

Isoleucine, Aspartate, and Leucine. The compound Imatinib moieties interact with the aminoacids Leu 1200, Asp1199, and Glu1202. The ligand interaction diagram and 3D representation have been depicted in **Figure 4**.

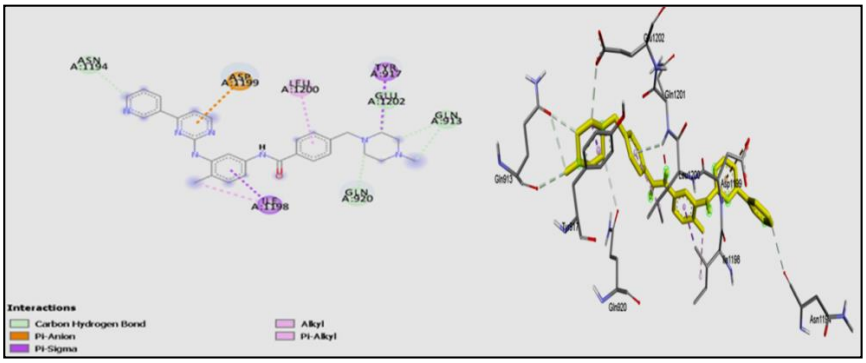


Figure 4. 2D and 3D Interactions of Imatinib with 6lxt spike glycoprotein.

Binding analysis and ligand interaction of Deoxywithaferin A

The ligand interaction and 3-D interaction of the compound Deoxywithaferin A with the 6LXT protein werefound to be -7.76 kcal/mol. The compound Deoxywithaferin A is found to be well associated with the active site aminoacids Tyr917, Leu1200, Ile1198, Asp1199, and Leu1197. The compound is well associated with Van-der-Waals interaction and hydrogen bonding interaction. The carbonyl moieties present in the compound arewell associated with the Positively charged aminoacids and non-polar aminoacids.

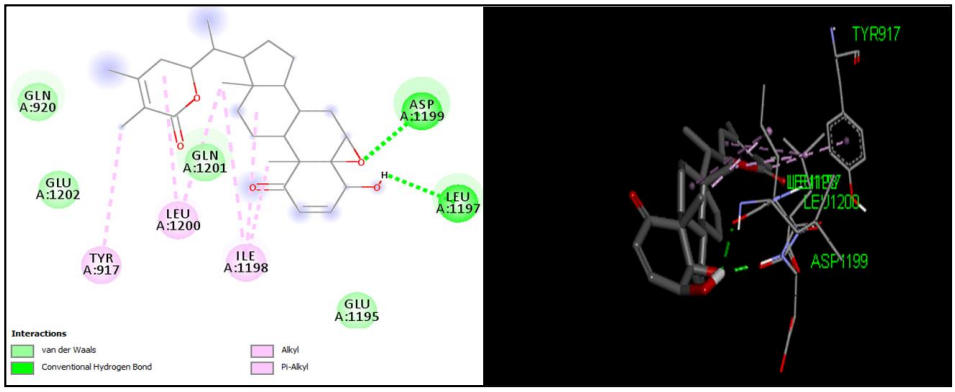


Figure 5. 2D and 3D Interactions of Deoxywithaferin A with 6lxt spike glycoprotein

Binding analysis and ligand interaction of Bosutinib

The compound Bosutinibwas found to interact with the Protein 6LXT of Covid-19 and revealed a docking score of -7.01kcal/mol. The compound was found to interact with Leu1200, Ile1198, and Non-polar interaction with Phe927. The carbonyl moiety present in the compound interacted with the aminoacid Asp1199. The nucleus of the compound has well occupied in the active site of the protein which reveals the good docking score. The 2D and 3D interactions of the compound with the ligand aredepicted in **Figure 6**.

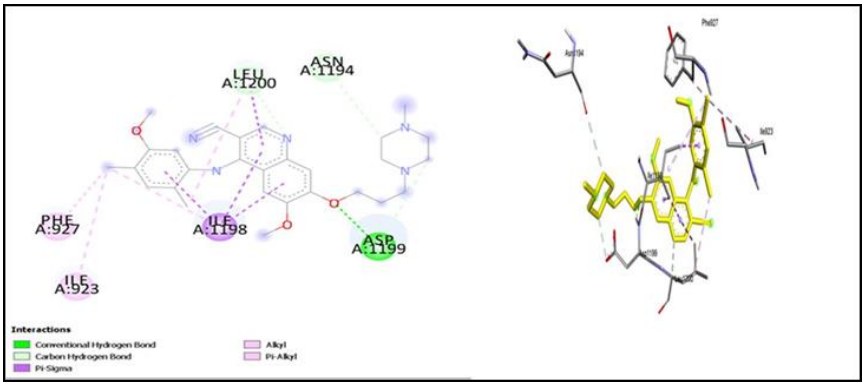


Figure 6. 2D and 3D Interactions of Bosutinib with 6lxt spike glycoprotein.

Binding analysis and ligand interaction of Atovaquone

The compound Atovaquone is well interacted with the protein 6LXT and found that the docking score of the compound is -7.06kcal/mol. The compound carbonyl moiety well interacts with Gln1201 and Gln920. The phenyl moieties of the compound well interact with the aminoacids Ile1090 and Tyr917. The hydrogen interaction in the phenyl moiety is found to interact with Ile1200. The 2D and 3D interaction was depicted in **Figure 7**.

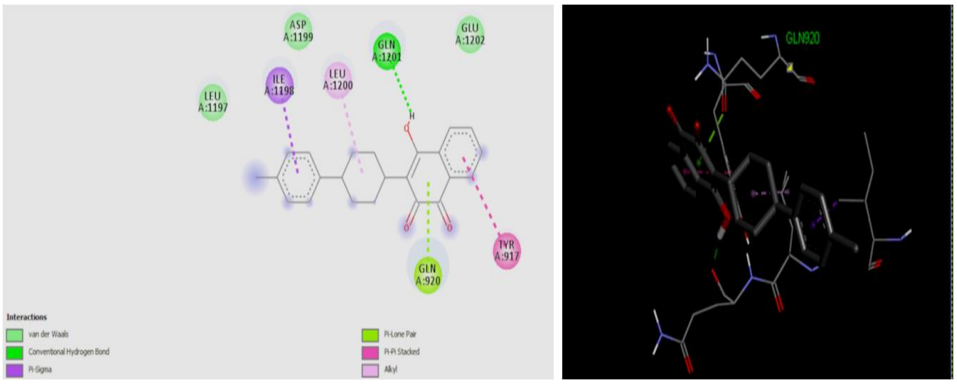


Figure 7. 2D and 3D Interactions of Atovaquone with 6lxt spike glycoprotein

Lipinski's rule of five

The compounds selected for our study have been done for their Pharmacokinetic properties. Most of the compounds have fallen into the ranges of Pharmacokinetics properties. The main properties of the drug-like compounds are Hydrogen bonding acceptor and Donar, Molecular Weight, Polarity value, and Molar Refractive index. Mostly the selected molecules have satisfied the Lipinski Rule of Five. So further with these compounds, in-vitro studies can be carried out for the effective use of drugs towards the SARS-Cov-19. **Table 2** represents the Lipinski rule of five for the Selected compounds for the study.

Table 2. Lipinski Rule of Five Properties for the selected compounds

		Lipinski's rule of five				
S.No	**Ligands**	**Mass (not more than five Dalton)**	**Hydrogen Bond donors(not more than 5)**	**Hydrogen bond acceptors (not more than 10)**	**LOGP(not more than five)**	**Molar Refractivity (should be Between 40-130)**
1.	Manzamine A	312	5	6	-0.053	77.145
2.	Imatinib	548	2	4	6.855	167.621
3.	Deoxywithaferin A	493	2	8	4.400	146.233
4.	Atovaquone	454	1	5	4.380	123.051
5.	Bosutinib	366	1	3	5.115	100.546
6.	Tetrandrine	530	1	3	4.349	137.932
7.	Shinpterocarpin	622	0	8	7.162	177.682
8.	3'hydroxy-4'methoxyglabridin	322	1	4	4.186	89.894
9.	Glabridin	354	2	5	4.009	98.446
10.	Ethyl Cholate	624	9	15	-1.015	147.095
11.	Raloxifene	436	3	2	3.927	119.034
12.	Arabidiol	473	2	5	6.075	136.251
13.	Pectolinarin	444	2	2	7.840	136.453
14.	Acronine	270	3	5	2.419	70.813
15.	Glyasperin A	321	0	4	3.736	92.623

16.	Avarol	422	4	6	5.322	118.655
17.	Liquirtin	314	2	2	5.439	94.568
18.	isoliquirtin	418	5	9	0.277	101.260
19.	propolis	418	6	9	0.172	103.973
20.	Liquirtigenin	438	2	8	3.952	113.455
21.	Morin	256	2	4	2.804	68.530
22.	Dehydroglyasperin C	302	5	7	2.010	74.050
23.	Herbacetin	354	3	5	4.253	100.931
24.	Khainoside B	302	5	7	2.010	74.050
25.	Amodiaquine	522	6	13	-0.260	129.777
26.	Diosmin	372	0	7	3.345	98.579
27.	Baicalein	608	8	15	-1.246	141.317
28.	Isoflavone	270	3	5	2.419	70.813
29.	Diadzein	222	0	2	2.997	66.014
30.	GlycyrrhizicAcid	254	2	4	2.713	69.149

CONCLUSION

The Compounds taken for the study are potentiallyin-capable to bind with the spike protein thus inhibiting the detrimental effects of the coronavirus on humans and other species. Among the three compounds chosen Manzamine A, which is been extracted from a marine sponge possesses a strong affinity forbinding. The drug can be taken orally but the intravenous path is preferable as compared to the oral path. The Top 5 Compounds chosen for the study have the potential to fight against the covid-19 infection by doing successful docking. Thus it can be concluded that the natural compounds could be potent drugs in combating covid-19 with further in-vitro and in-vivo characterization studies.

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