IJMPR 2021, 5(4), 328-334

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

DOCKING STUDY OF FDA-APPROVED DRUGS AND MODIFIED DERIVATIVES ON HUMAN CORONAVIRUS PAPAIN-LIKE PROTEASES (4OVZ)

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Received on: 02/07/2021
Revised on: 22/07/2021
Accepted on: 12/08/2021

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ABSTRACT

The COVID-19 outbreak is a matter of concern worldwide due to unavailability of promising treatment comprising medication or vaccination till date. The discovery of antiviral drug is of immense importance in the existing spread of novel coronavirus. The goal of the present study was to evolve an opposite antiviral drug against the novel COVID-19 virus. A directly succeeding perspective would be to use the prevailing influential drugs from several antimicrobial and chemotherapeutic agents. The encouraging approach is to identify promising drug molecules and compounds through virtual screening via molecular docking of FDA-approved drugs and some derivatives for probable therapeutic outcome.

KEYWORD: A directly succeeding perspective would be to use the prevailing influential drugs from several antimicrobial and chemotherapeutic agents.

INTRODUCTION

Coronavirus disease (COVID-19) is a communicable disease caused by a newly discovered coronavirus. Major symptoms include respiratory illness with high fever and dry cough. WHO declared COVID as a pandemic and world's scientist and global health professionals involved in research to find effective medicine.[1] docking is a term used for computational schemes that attempt to find the "best" matching between two molecules, a receptor and a ligand. Molecular docking programs screen chemical databases for novel ligands that fit protein binding sites. When one compound fits the site well, close analogs typically do the same, so many of the compounds that are found in such screens resemble one another, thus reducing the variety and novelty of the compounds suggested. Docking process includes both of prediction of ligand conformation and of orientation which means posing within a targeted binding site. The docking studies have two important aims, namely, are accurate structural modelling and correct prediction of activity. Mankind has formerly witnessed the outburst of numerous deadly pathogens such as Zika, Ebola, the Middle East respiratory syndrome (MERS) coronavirus, severe acute respiratory syndrome (SARS) coronavirus, and, currently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2-6] Virtual screening is a prevalent modelling tool broadly employed in structure-based drug design.[7-9] It is an imperative means to predict the binding affinity, type of interaction, and the suitable receptor-binding sites among the drug and corresponding receptor by using, for example, scoring functions.

Dock score=a×vdW+b×Coul+Hbond+Metal+Lipo+BuryP+RotB+Site

Where, a and b are co-efficient constant for vdW and Coul, respectively. vdW = van der Waals energy; Coul = Coulomb energy; Hbond = Hydrogrn bonding with receptor; Metal = Binding with metal; Lipo = Constant term for lipophilic; BuryP = Buried polar group penalty; RotB = Rotatable bond penalty; Site = active site polar interaction.[20]

In protein data bank three dimensional receptor targets are already available on SARS-CoV-encoded cysteine proteases, 3CLpro(chymotrypsin-like protease) and PLpro (papain-like protease).[10] Papain like protease involved in polyprotein replication in corona virus.[11] The function of PLpro include processing of the viral polyprotein,[12] deubiquitination[13] (the removal of ubiquitin), and deISGylation[14] (The removal of ISG15) from host-cell proteins. These last two enzymatic activities result in the antagonism of the host antiviral innate immune response.[15] Papain-like protease divided into catalytic and ubiquitin domain, the first one is the interesting part in terms of enzymatic functions, as well as inhibiting the protein. It may be further divided into three subdomains: thumb, palm, and fingers (Figure 1A). The active site is located between palm and thumb, utilizing three main residues, called the catalytic triad: Cys111, His272, and Asp286.[16] Native ligand N-[(4-fluorophenyl)methyl]-1-[(1R)-1-naphthalen-1-ylethyl]piperidine-4-carboxamide binds adjacent to the active site at the enzyme S3−S4 subsites.[17,18] exclusive of any interactions with the catalytic triad (Cys112-His273-Asp287). Upon inhibitor binding, the β-turn/loop

(Gly267-Gly272) containing Tyr269 adopts a closed conformation via an induced-fit mechanism to interact with the inhibitors. This enables the formation of a 3 Å H-bond between the backbone carbonyl of Tyr269 and the carboxyamide nitrogen of the inhibitors. An additional and important interaction is observed between the piperidine ring nitrogen and the side chain carboxylate of Asp165. The puckering of the piperidine ring positions the cationic nitrogen within a distance of 2.8 Å from oxygen of the carboxylate of Asp165, thereby forming a charge-to-charge mediated H-bond.[19]

Human coronavirus Papain-Like proteases (4OVZ)

Fig. 1: 4OVZ Cartoon representation with pymol molecular viewer.

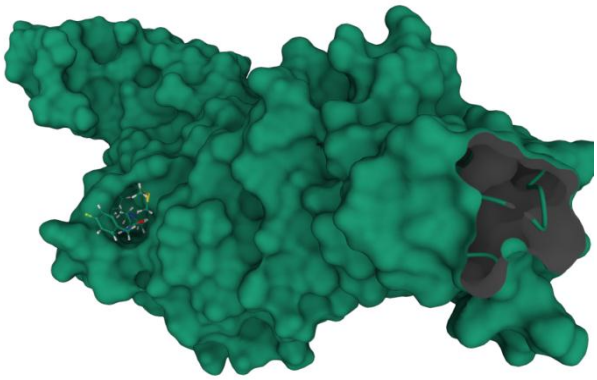


Fig. 2: 4OVZ Molecular surface representation.

It is cocrystallized structure with N-[(4-fluorophenyl) methyl]-1-[(1R)-1-naphthalen-1-ylethyl] piperidine-4-carboxamide. Molecular docking is utilized to predict interactions of macromolecule and ligand. This prediction is used to screen structural libraries to develop new lead molecule and to study minimum energy confirmation.[9]

MATERIALS AND METHODS

Human Coronavirus Papain-Like Proteases and compounds are docked to find out protein-ligand interactions, binding mode and affinity.

Proteins

The protein structure of Human Coronavirus Papain-Like Protease (PDB cod: 4ovz) Was selected because it is available with co-crystallized ligand N-[(4-fluorophenyl)methyl]-1-[(1R)-1-naphthalen-1-ylethyl]piperidine-4-carboxamide**,** 4ovz was obtained From The protein data bank and protein structure prepared in auto dock vina software by removing water molecule, chain B and adding polar hydrogen, Kollman charges And grid dimensions were obtained by labelling co-crystallized inhibitor and adjusting grid box on labelled inhibitor, crystal structure is optimized by removing native ligand N-[(4-fluorophenyl)methyl]-1-[(1R)-1-naphthalen-1-ylethyl]piperidine-4-carboxamide,and re-docked on 4ovz, it is found that it is interacting with same amino acids Asp165 and Tyr269 which are adjacent to the active site.

Grid box dimensions were used

center_x = -14.792429, center_y = 46.108089, center_z = -40.410036

size_x = 20, size_y = 20, size_z = 20

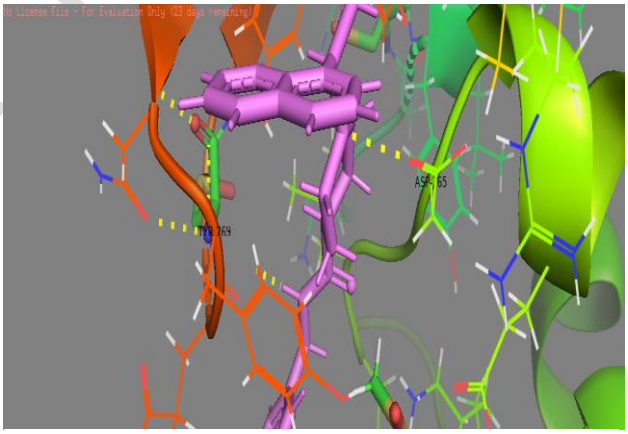


Fig. 4: After Re-docking, Interaction of native ligand P85 with Asp165 and Tyr269.

Table no. 1: Re-docking Result and Confirmations of native ligand P85 with autodock vina.

Mode	Affinity | (kcal/mol)	Dist from best mode	
		rmsd l.b.|	rmsd u.b.
1	-9.7	0.000	0.000
2	-9.3	5.473	9.895
3	-8.6	4.239	6.897
4	-8.5	0.561	2.252
5	-8.4	3.572	6.536
6	-8.3	4.951	8.317
7	-8.3	6.478	9.982
8	-8.0	3.526	6.655
9	-7.7	4.372	10.480

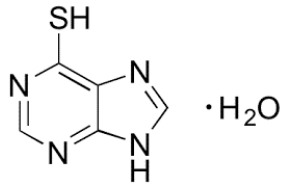
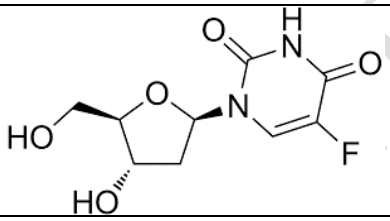
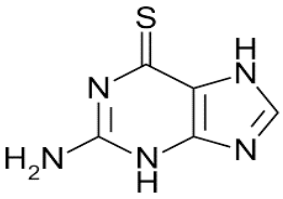
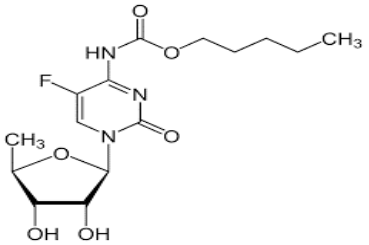
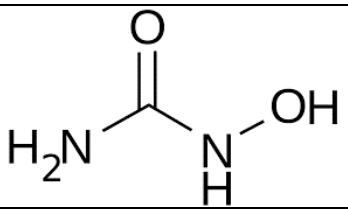
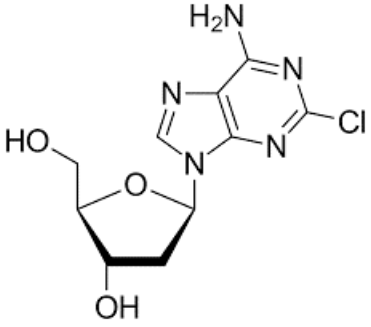
Ligands

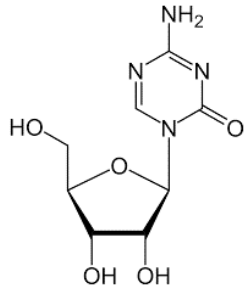
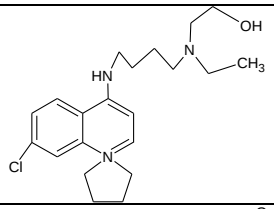
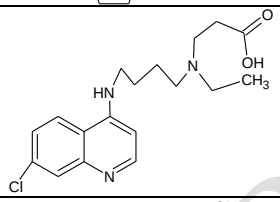
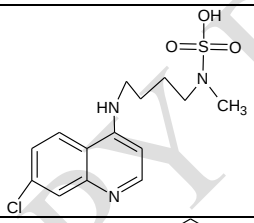
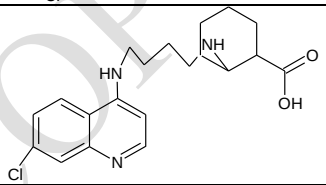
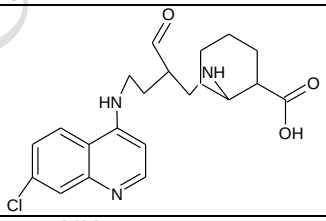
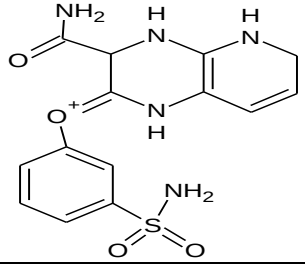
The Structures of ligand molecule were obtained from pub-chem database in sdf format and then these structures were converted to pdb format with open bable. with Auto-dock vina all structures converted into pdbqt format, and docked on prepared 4ovz protein structure.

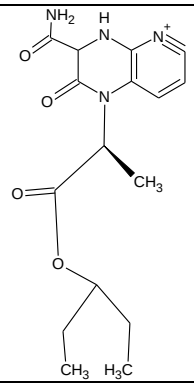
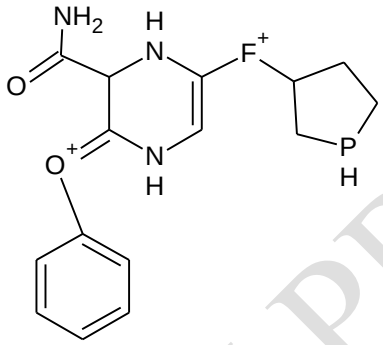
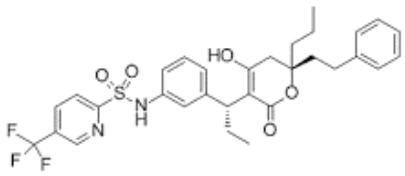
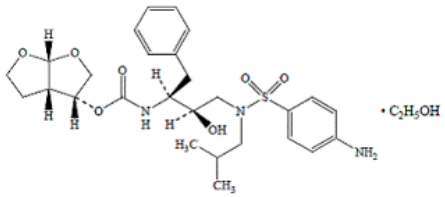
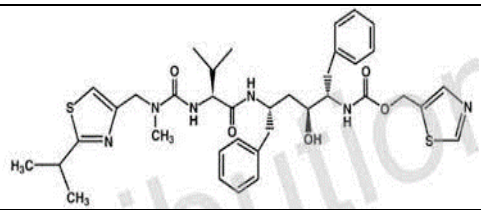
Protein-ligand docking

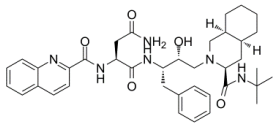
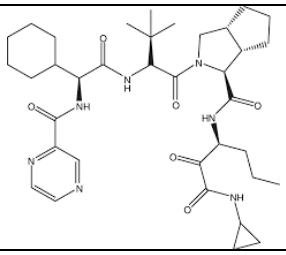
The protein and ligand structures converted into Pdbqt format with auto-dock vina, configuration file were prepared with grid dimensions and with the command prompt, all the compounds were docked and docking score given in table no 2. The results less than 1.0 Å in positional root-mean-square deviation (RMSD) was clustered together and represented by the result with the most favourable free energy of binding. The pose with lowest energy of binding or binding affinity was extracted and aligned with receptor structure for further analysis.

Table no. 2: Docking Score of 20 compounds (highlighted text indicate good affinity with receptor).

Sr. no.	Name of derivatives	Structure	Docking score/ Affinity | (kcal/mol)
Lig 1	6-Mercaptopurine hydrate		**-5.5**
Lig 2	Floxuridine		-6.7
Lig 3	Thioguanine		-6.1
Lig 4	Capecitabine		-6.2
Lig 5	Hydroxyurea		-6.3
Lig 6	Cladribine		-6.2

Lig 7	Azacitidine		-5.6
Lig 8	Chlroquine1		-8.7
Lig 9	chlroquine2		-8.7
Lig 10	Chlroquine3		-9.2
Lig 11	Chlroquine4		-9.2
Lig 12	Chlroquine5		-9.2
Lig 13	Favinapir 1		-6.8

Lig 14	Favinapir 2		-6.5
Lig 15	Favinapir 3		-8.8
Lig 16	Tipranavir		-8.7
Lig 17	Darunavir		-7.1
Lig 18	Ritonavir		-9.1
Lig 19	Saquinavir		-11.5

			
Lig 20	Telaprevir		-9.1

Analysis

The results are identified to have inhibitory activities against novel COVID-19 protease Results were viewed and analysed with PyMOL molecular viewer. Saquinavir, Chlroquine, Ritonavir shows high affinity with protease (4ovz).

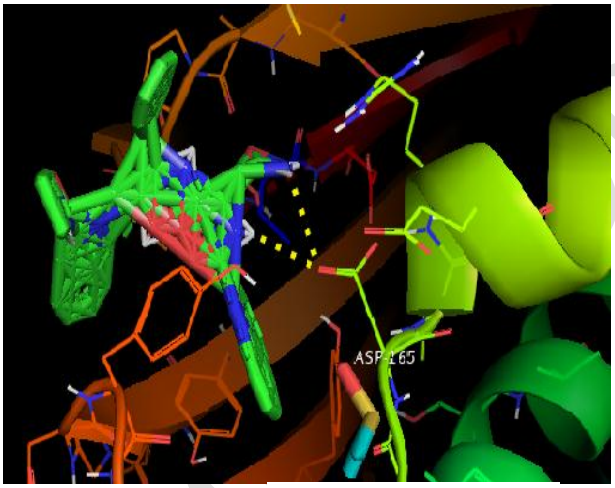


Fig. Interaction of Saquinavir with ASP 165.

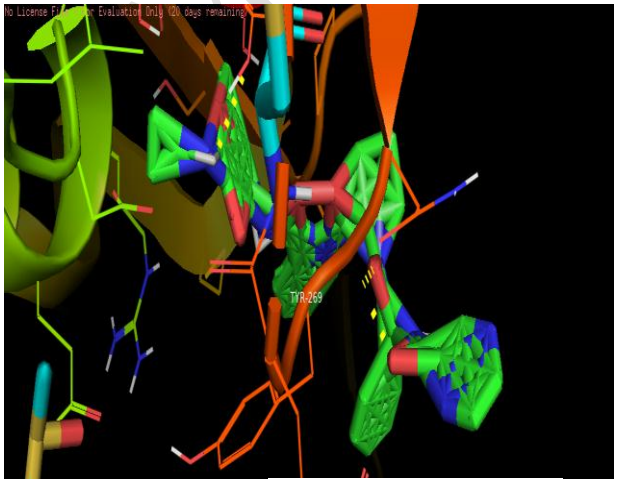


Fig. Interaction of Telaprevir with TYR 269.

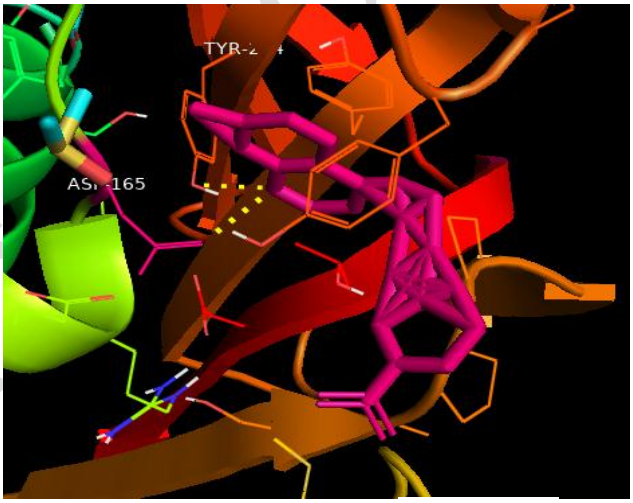


Fig. Interaction Chloroquine with ASP 165.

CONCLUSION

Finally, with due attention to the, we can conclude that these compounds may be considered as effective COVID 19 antiprotease drugs.

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