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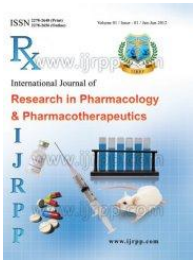

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Bedaquiline-A potential inhibitor of COVID-19 main protease based on molecular docking

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ABSTRACT

A new coronavirus (CoV) identified as COVID-19 virus is the etiological agent responsible for the 2019-2020 viral pneumonia outbreak that commenced in Wuhan. Currently there is no targeted therapeutics and effective treatment options remain very limited. Here, we have studied the virtual interaction between COVID-19 protease (PDB ID: 6LU7) and commercially available drug molecules by molecular docking using Autodock 4.2. The commercially available drug molecules are selected by ligand-based pharmacophore search using PharmaGist web server considering tideglusib as lead molecule. The drug molecule Bedaquiline was identified as potential inhibitor of COVID-19 Mpro (PDB ID: 6LU7) which shows higher binding affinity (-9.06 kcal/mol) than the lead Tideglusib (-8.48 kcal/mol). However, these data need further in vitro and in vivo evaluation to repurpose the bedaquiline against 2019-nCoV. We propose that this drug can be used as therapeutic agents/biomarker in this case.

Keywords: Covid 19, Bedaqualine, 6LU7, Docking, Pharmacophore

INTRODUCTION

The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China and spread around the world. Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses; therefore bats could be the possible primary reservoir. The intermediate source of origin and transfer to humans is not known, however, the rapid human to human transfer has been confirmed widely. There is no clinically approved antiviral drug or vaccine available to be used against COVID-19. However, few broad-spectrum antiviral drugs have been evaluated against COVID-19 in clinical trials, resulted in clinical recovery [1].

On February 6, 2020, worldwide protein data bank has established COVID-19 coronavirus

resources to facilitate target based drug design efforts against current global threat [2]**.** Latter COVID-19 virus main protease Mpro (PDB ID: 6LU7) was found as key CoV enzyme, which plays a pivotal role in mediating viral replication and transcription, making it an attractive drug target for this virus[3,4]**.** This study aims to identify the potential inhibitor of COVID-19 Mpro (PDB ID: 6LU7) through ligand-based pharmacophore search and molecular docking. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding model(s) of a ligand with a protein of known three-dimensional structure [5].

MATERIALS AND METHODS

Proteins/Macromolecules

COVID-19 Mpro (PDB ID: 6LU7) structures were obtained from PDB (https://www.rcsb.org/), in .pdb format. PDB is an archive for the crystal structures of biological macromolecules, worldwide. The 6LU7 protein contains two chains, A and B, which form a homodimer. Chain A was used for macromolecule preparation. The native ligand (N3) for 6LU7 is n-[(5-methylisoxazol-3-yl)carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3-yl]methyl}but-2-enyl)-l-leucinamide. N3 is a potent irreversible inhibitor of COVID-19 virus Mpro. The residues of 6LU7 interact with inhibitor N3 are PHE140, ASN142, GLY143, CYS145, HIS163, HIS164, GLU166, GLN189, and THR190. These residues are considered as key residues forming the binding pocket [6]. The interactions between COVID-19 Mpro and native ligand N3 is given as 2D image in Figure1.

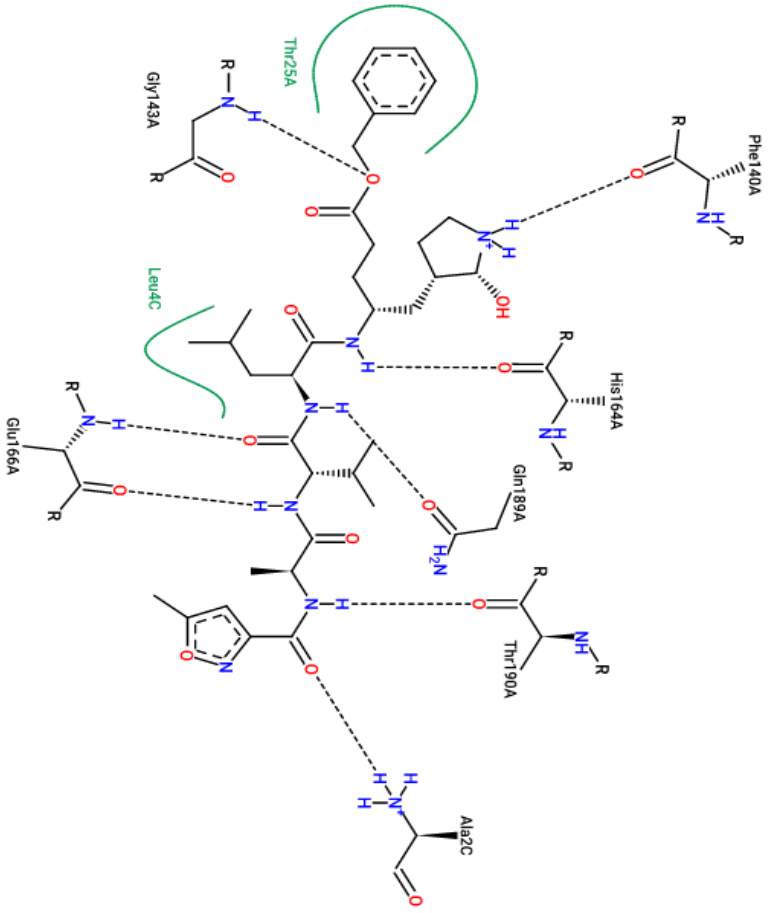
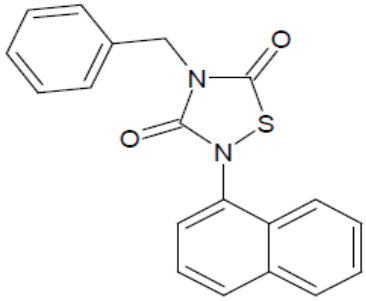


Figure 1: The interactions between COVID-19 virus Mpro and native ligand N3.

Lead Molecule

Tideglusib was identified by Jin, Z. et al. as drug lead which inhibits COVID-19 Mpro (PDB ID: 6LU7). The inhibitor tideglusib was identified through the high throughput screening is likely to occupy the same pocket as N3. [6] So, Tideglusib is considered as Lead molecule in the current study and the structure of the same is given in Figure 2.

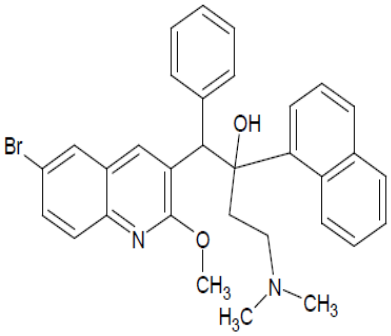


Tideglusib

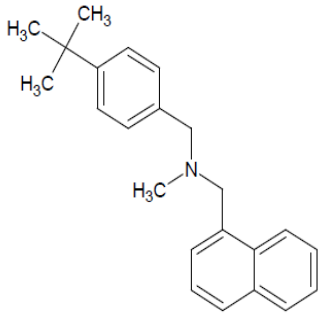
Figure 2: Structure of Tideglusib.

Detection of Pharmacophore candidates

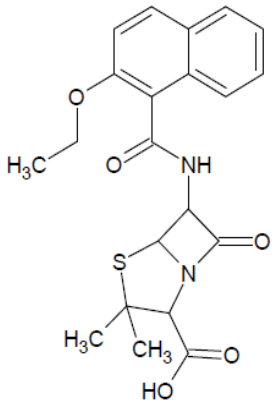
PharmaGist, a freely available web server (https://bioinfo3d.cs.tau.ac.il/PharmaGist/) for pharmacophore detection. A pharmacophore is the spatial arrangement of features that enables a molecule to interact with a target receptor in a specific binding mode. The input of set of drug-like ligands with Lead molecule (in 3D representation) in PharmaGist server will provide list of candidate pharmacophores based on 3D superposition of conformations of input ligands that share it [7]. The selected lead molecule tideglusib (4-benzyl-2-(naphthalen-1-yl)-1,2,4-thiadiazolidine-3,5-dione) have naphthalene and thiadiazolidine rings. Various naphthalene and thiadiazole based commercially available drug molecules were selected randomly and the 3D structures of the selected ligands and Tideglusib were obtained from the pubchem website (https://pubchem.ncbi.nlm.nih.gov/) in the .SDF format. Further, the ligands were optimized using the Avogadro version 1.2, with Force Field type MMFF94, and saved in .mol2 format[8]**.** Then all the individual .mol2 Files are zipped as single Zip file and submitted in PharmaGist to detect the pharmcophore candidates. The best 5 Ligands are selected based on score obtained by pairwise alignment in PharmaGist. The structure and pairwise alignment with lead tideglusib of the selected ligands are given in Figure 3 and Figure 4 respectively.



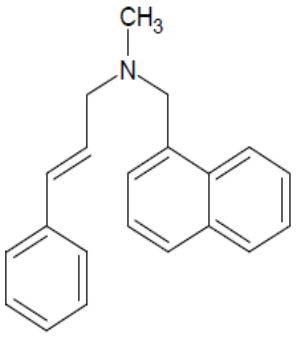
Bedaquiline



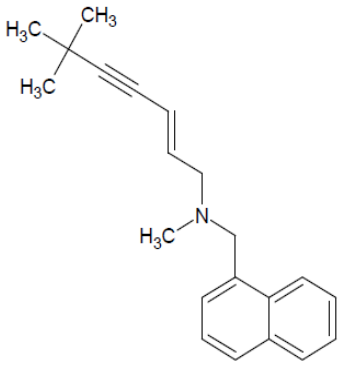
Butenafine



Nafcillin

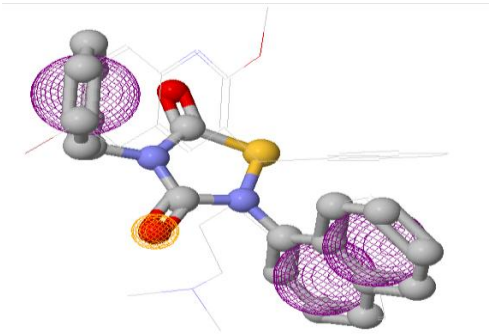


Naftifine

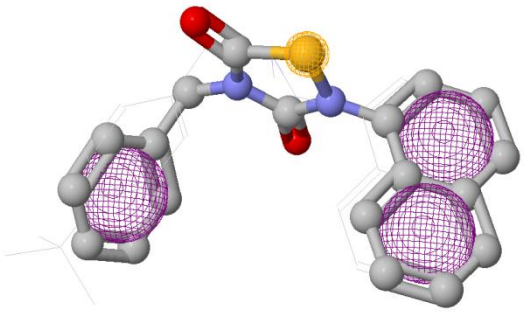


Terbinafine

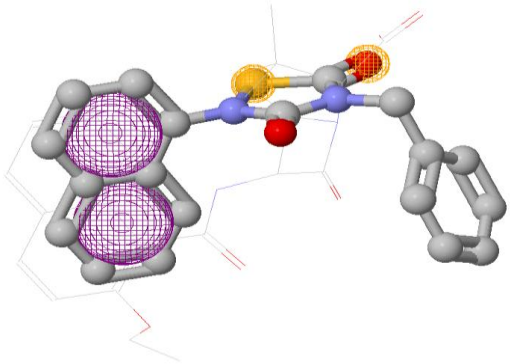
Figure 3: Structures of selected Ligands



Bedaquiline



Butenafine



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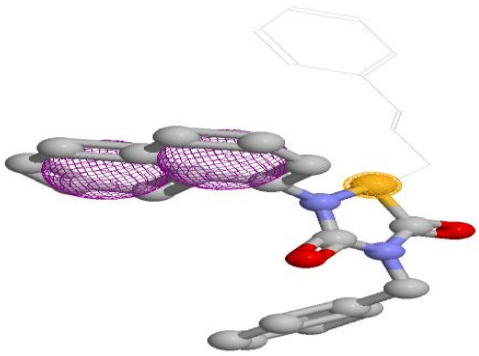

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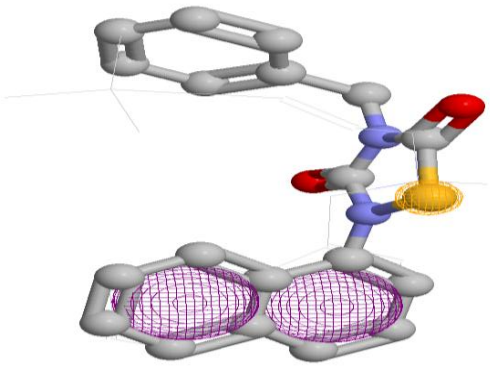


Terbinafine

Figure 4: Pairwise-alignment of Tideglusib and selected ligands. Tideglusib displayed as ball and stick model and ligands are displayed as Wire model. .

Aromatic **Hydrogen bond acceptor**

The output .mol2 file obtained through PharmaGist was submitted to the ZINCpharmer server to visualize the alignment of the ligand with lead molecule [9]. The aligned structures shares pharmacophoric characteristics as given in the Table 1.

Table 1: Pharmacophoric characteristics of Selected Ligands

Lead (Pivot) molecule	Ligand	Score	Features	Spacial Features	Aromatic	Hydro phobic	H Bond Donor	H Bond Acceptor
Tideglusib	Bedaquiline	10.52	4	4	3	0	0	1
Tideglusib	Butenafine	10.52	4	4	3	0	0	1
Tideglusib	Nafcillin	9.02	4	4	2	0	0	2
Tideglusib	Naftifine	7.52	3	3	2	0	0	1
Tideglusib	Terbinafine	7.52	3	3	2	0	0	1

Optimization of the Geometry of Selected Ligands

The 3D structures of the selected ligands were obtained from the https://pubchem.ncbi.nlm.nih.gov/ website in the .SDF format. Further, the ligands were optimized using the Avogadro version 1.2, with Force Field type MMFF94, and saved in .mol2 format [8].

Molecular Docking

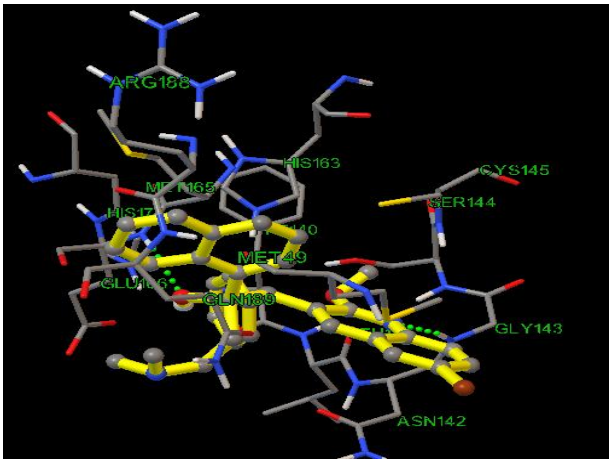
Molecular docking was performed by the AutoDock program version 4.2. Autodock 4.2 was supported by Autodock tools, MGL tools, and Rasmol. For docking, the protein was prepared by removing all water molecules, heteroatoms, ligand and co-crystallized solvent. Polar hydrogens and partial charges were added to the structure using Autodock tools (ADT) version 1.5.6. Co-crystallized inhibitor (N3) has been removed [10]. The file was saved in the .PDBQT format for further analysis. The amino acids in the active site of the macromolecule were selected and the grid box was used to obtain the X, Y and Z coordinates. The ligand files in the .mol2 format were converted to the PDBQT format after detecting the torsion root.

Using the protease .PDBQT file, ligand .PDBQT file and the X, Y and Z coordinates, binding affinity was calculated using AutoDock 4.2. The 3D structure of the target-ligands interaction was visualized using AutoDock 4.2. We used Lead, Tideglusib as a positive control. The molecular docking analysis results of selected ligands against COVID-19 Mpro (PDB ID: 6LU7) are listed in Table 2.

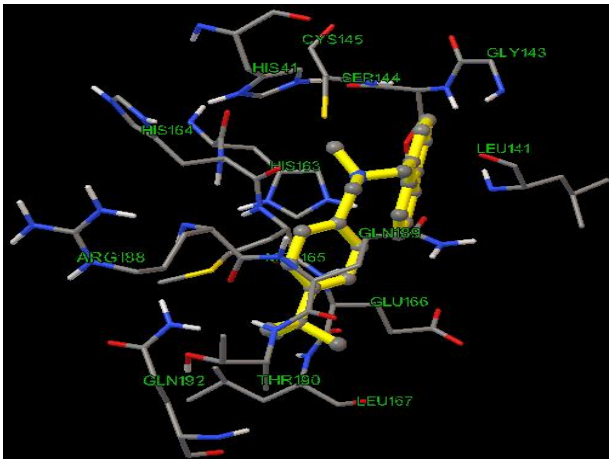
Table 2: Molecular docking analysis results of selected ligands against 6LU7

Ligand Name	Binding Energy (kcal/mol)	No. of Hydrogen bonds formed	Interacting Residues	Ligand Efficiency (kcal/mol)	Inhibition Constant (µM)	Inter molecular Energy (kcal/mol)	VDW-H Bond Desolvation Energy (kcal/mol)
Bedaquiline	**-9.06**	**2**	**GLY143, GLU166**	**-0.24**	**228.83**	**-11.74**	**-11.26**
Butenafine	-8.18	-	-	-0.34	1.01	-9.67	-9.32
Nafcillin	-7.38	2	GLU166, GLN189	-0.25	3.9	-9.17	-9.24
Naftifine	-7.67	-	-	-0.35	2.41	-9.16	-8.88
Terbinafine	-7.48	-	-	-0.34	3.3	-9.27	-9.06
Tideglusib (Positive control)	-8.48	-	-	-0.35	611.62	-9.37	-9.39

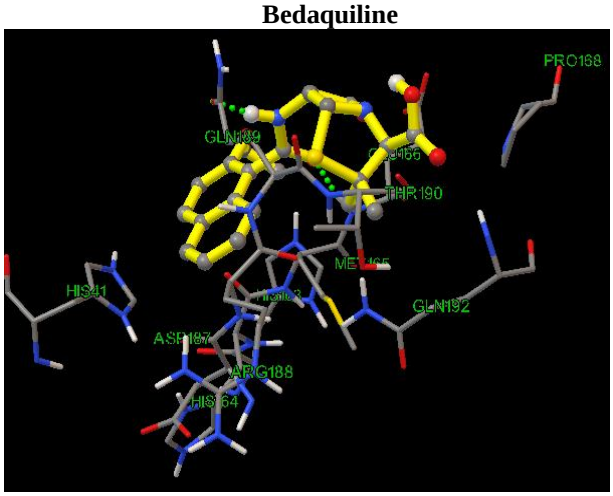
The detailed view of interactions between selected ligands and COVID-19 virus Mpro (PDB ID: 6LU7) are given in Figure 5. The docking pose of selected ligands to COVID-19 virus Mpro (PDB ID: 6LU7) are given in Figure 6.



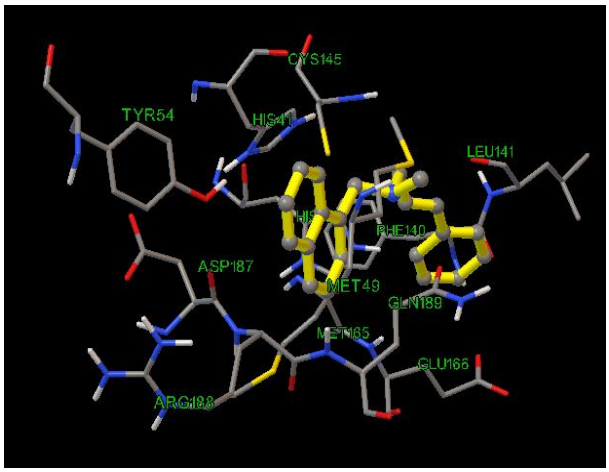
Bedaquiline



Butenafine



Nafcillin



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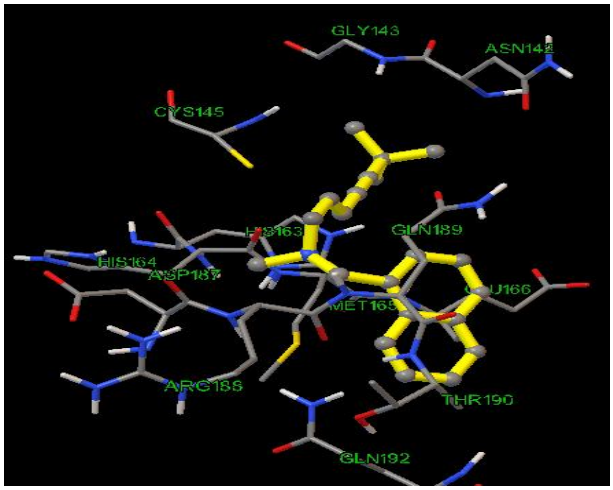
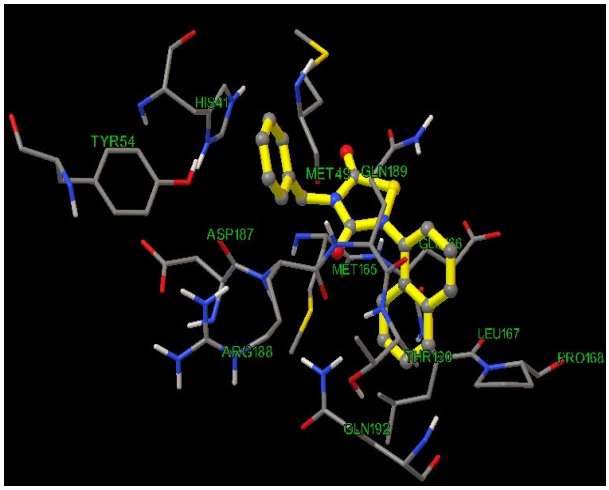
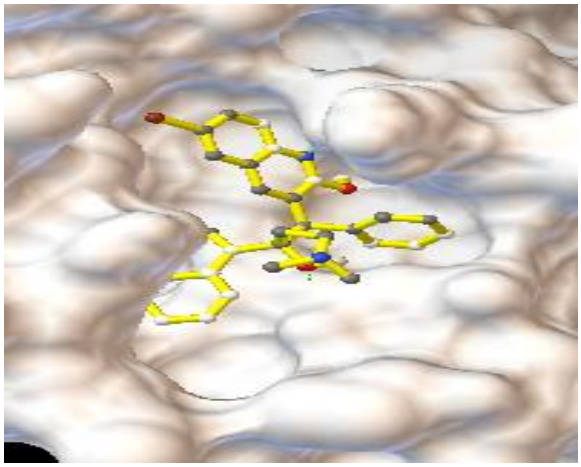


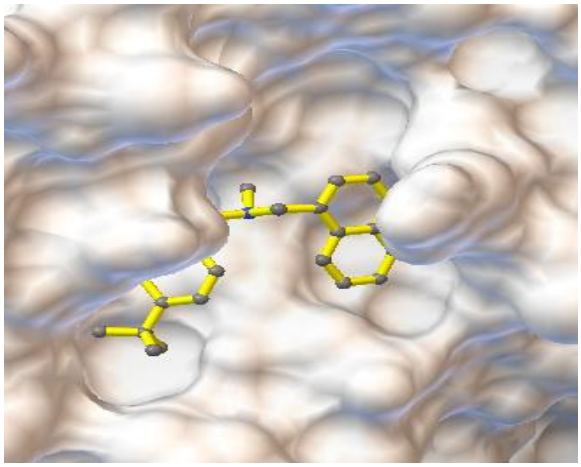


Terbinafine **Tideglusib (Positive Control)**

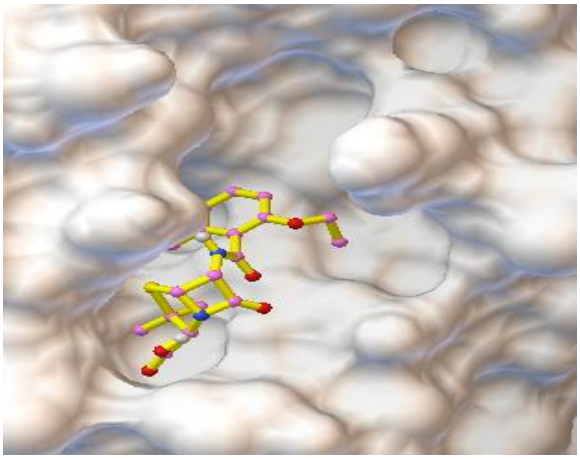
Figure 5: 3D images of COVID-19 virus Mpro (PDB ID: 6LU7) -ligand interactions.



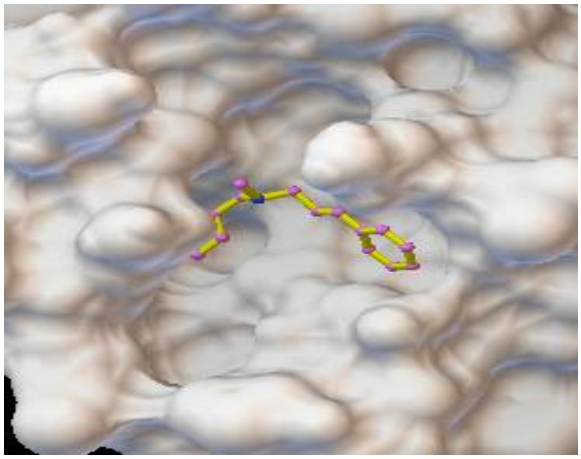
Bedaquiline



Butenafine



Nafcillin



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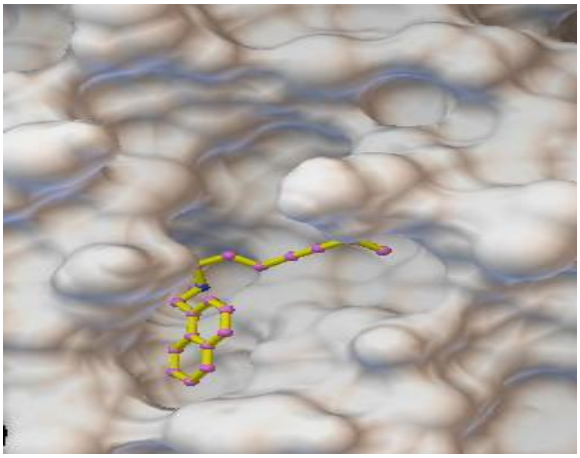

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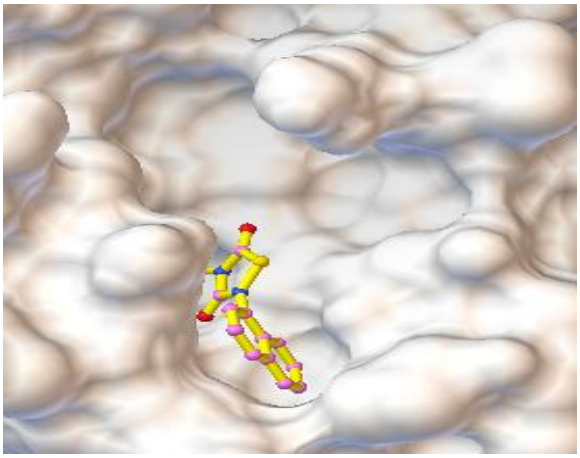

Tideglusib (Positive Control)

Figure 6: Docking pose of selected ligands to COVID-19 virus Mpro (PDB ID: 6LU7)

RESULTS AND DISCUSSION

All the five selected ligands were docked against COVID-19 virus Mpro (PDB ID: 6LU7). Figure 5 shows the docked images of selected candidate ligands including the considered lead compound tideglusib. In-silico studies revealed all the selected ligands showed good binding energy toward the target protein ranging from -7.38 kcal/mol to -9.06 kcal/mol which are lesser than the upper threshold (–6 kcal/mol), generally regarded as a cut-off in ligand-binding studies [11]. Especially the ligand bedaquiline showed higher binding affinity (-9.06 kcal/mol) than the lead tideglusib which is considered as potential drug candidate in the study. The binding affinity of the lead cmpound, Tideglusib was -8.48 kcal/mol. Moreover, all the selected ligands showed less inhibition constant value (µM) than the lead tideglusib which further reveals that the selected ligands are potent than the lead tideglusib. The 3D visualization of binding (Figure 5 & 6) of the selected ligands confirms that each of the ligands are likely to bind the same active pocket of the COVID-19 virus Mpro (PDB ID: 6LU7) as native ligand N3 and Lead Tideglusib.

CONCLUSION

There may be a number of molecules will show higher affinities toward COVID-19 virus Mpro (PDB ID: 6LU7). But due to the emergency situation arising in the world, it is preferred to choose commercially available drugs. In the present study, we identified bedaquiline as a potentital inhibitor of COVID-19 virus Mpro (PDB ID: 6LU7) based on molecular docking. Further in vitro and in vivo evaluations are required to repurpose the bedaquiline against 2019-nCoV. Moreover, the binding pose of all selected naphthalene based drug molecules reveals the selectivity towards the target active site of native ligand N3. This, further conclude that the naphthalene analogue is a building block for developing drugs against COVID-19. The findings of the present study will provide opportunities to other researchers to identify the right drug to combat COVID-19.

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