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MOLECULAR DOCKING ANALYSIS OF FDA APPROVED ANTICANCER DRUG AGAINST SARS COVID-19

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ABSTRACT:

The aim of the present study is to identify the efficacy of FDA approved anticancer drugs against COVID-19. The COVID-19 virus main protease, a key CoV enzyme which plays a vital role in viral replication and transcription. Docking studies were performed using Glide for CoV enzyme and selected anticancer drugs. Out of 14 compounds five showed better inhibitory activity than the antiviral drugs favipiraivir and umifenovir which are currently used in COVID treatment. Inhibiting the central dogma of CoV enzyme might be an effective treatment for COVID. Hence it is suggested that Entrectinib which had better inhibitory activity can be used for the treatment.

KEYWORD: FDA Approved Anticancer drugs, COVID-19, CoV enzyme, Glide, Entrectinib.

INTRODUCTION

A severe outbreak of a novel corona virus called as COVID-19 was reported in Wuhan China in December 2019 which mainly affect the respiratory track ***(Huang et al.,2020).*** The infection rapidly spread across the whole world and has become a vital causative agent for the disease ***(Phan et al,.2020).*** The incubation period of corona virus is approximately 1 to 14 days, with varying symptoms from patient to patient. Patients with past medical history of asthma, diabetes, heart ailment and elderly people, children below 6 years and individuals with weaker or compromised immune systems are at high risk to this disease (***Shah et al.,2020).*** Investigation briefly describes person-to-person transmission in both hospital and family ***(Chan et al.,2019).*** Main protease (Mpro), a key enzyme of corona virus which plays a pivotal role in

arbitrating viral replication and transcription (***Jin et al.,2020)*** inhibiting the activity of this enzyme would block viral replication ***(Zhang et al., 2020).***

The present study employs an *in silico* docking approach to understand the mechanism of FDA approved anti-cancer drugs against COVID-19. The docked compounds were compared with the antiviral drugs favipiraivir and umifenovir which are currently used in COVID treatment.

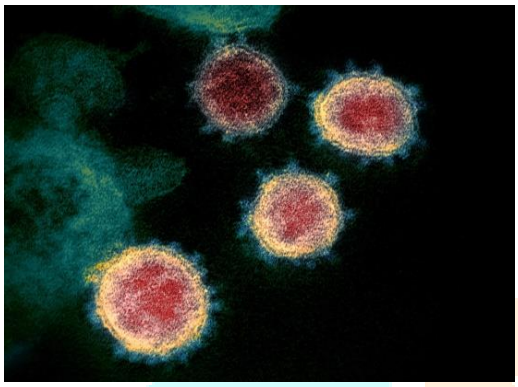

Fig 1. Novel Coronavirus of SARS COVID-19

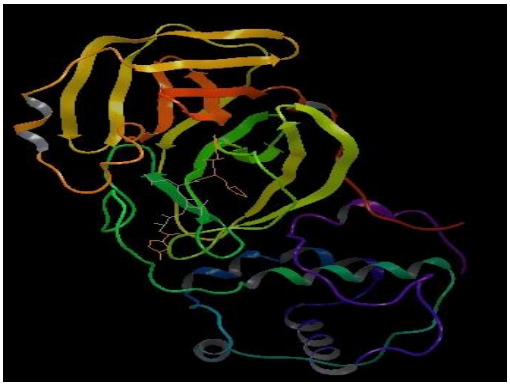

Fig 2. Complex structure of COVID-19

MATERIALS AND METHODS

Retrieve of the protein structure

The 3-D structure of COVID-19 main protease in complex with N3 inhibitor was retrieved from the Protein Data Bank. (PDB) is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids ***(Berman,et.al 2008).***

Binding Site Prediction

The binding/active site of the receptor COVID-19 main protease was identified using PDBSum. It is a pictorial database which shows the molecule that make up of the structure (*i.e.* protein chains, ligands and metal ions) and schematic diagrams of their interactions. The PDB ID of the target protein was given as input in the search box available at the homepage.

Preparation of ligand structures

The FDA approved oncology drugs were used for docking studies. The structures of the compounds are retrieved from PubChem database.

Docking analysis

Docking analysis of the receptor and ligand molecules is done using Grid based Ligand Docking with Energetics (GLIDE). Glide automatically generates conformation for each input ligand and can run flexible docking **(*Richard et al.,2004*).** Docking analysis was carried out for the receptor COVID-19 main protease with selected oncology drugs and the trial inhibitor for COVID using glide software.

RESULTS

***In silico* Analysis**

3D structure of acetylcholinesterase

The structure of COVID-19 main protease in complex with N3 inhibitor was retrieved from the Protein Data Bank (PDB ID: 6LU7) **(Figure 1)** and the sequence length is 306 AA and the resolution of the structure is 2.16 Å

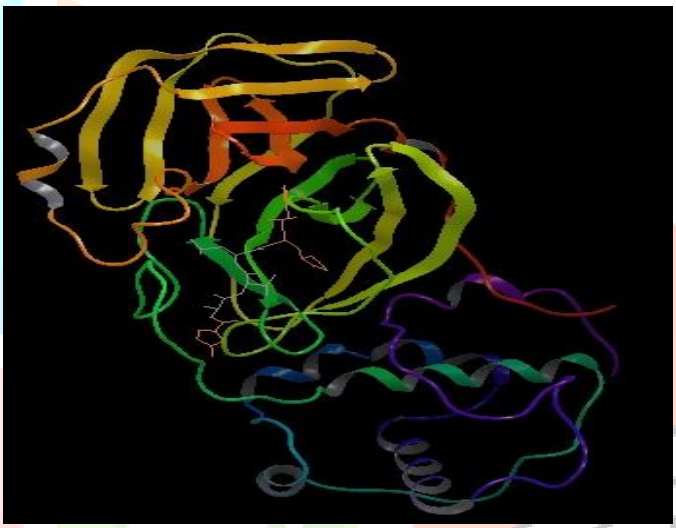

Figure 1. Complex structure of COVID-19 main protease in complex with N3 inhibitor

Binding Site Prediction

Binding site residues of COVID-19 main protease are THR190, GLA189 CYS145, PHE140, HIS163, VAL3,GLY143 , GLU166 retrieved from the PDBSum **(Figure 2).**

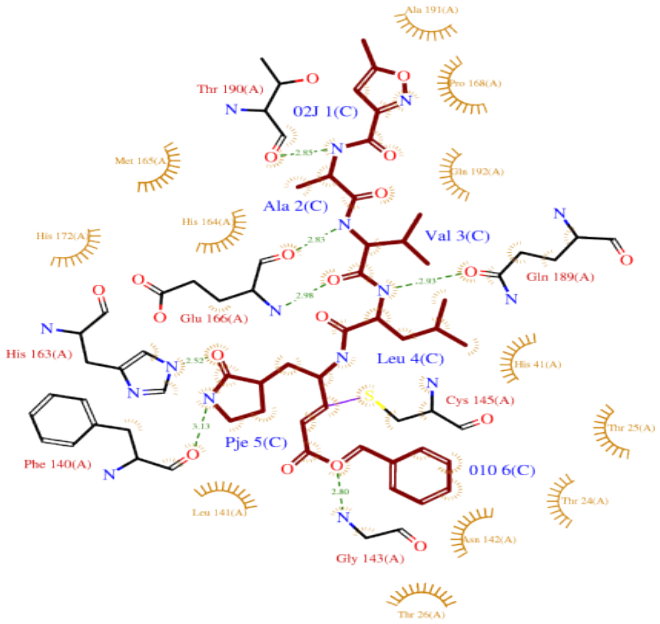

Figure 2. Active site region of COVID-19 main protease

Docking Analysis

The selected compounds were docked with the 3D structure of COVID-19 main protease using GLIDE**.** The docked compounds were compared with the antiviral drugs. The compounds with better results than the drug were identified based on Glide Score (G-Score) and tabulated **(Table 1).** Glide Score is predicted based on the lipophilic, hydrophobic interactions, hydrophobically packed H-bonds, electrostatic interactions and low molecular weight. Lower the Glide score confirms the better binding affinity.

Table 1. Glide Score, Hydrogen Bond Interaction and Bond length of the docked complexes of Anti-viral compounds and Onco-drugs

S.No.	Drugs/Compounds	PUBCHEM Compound CID	Glide Score (Kcal/mol)	Interactions (D-H…O)	Bond length (Å)
Anti-viral drugs					
1	UMIFENOVIR	131411	**-3.525902**	(O-H…O)ASN142	1.913
2	FAVIPIRAVIR	492405	**-3.288208**	(N-H…O)THR25 (O…H-O)THR24	1.896 1.958
Oncology-drugs					
1	ENTRECTINIB	25141092	**-5.162581**	(N-H…O)GLU166 (N-H…O)GLU166 (N-H…O)GLU166 (N-H…O)GLY138	2.038 2.336 1.844 2.447
2	FEDRATINIB	16722836	**-4.401312**	(N…O-H)SER139 (N-H…O)GLY138	2.159 2.015
3	PEMIGATINIB	86705695	**-3.811409**	(O…H-N)ASN142 (N-H…O)GLU166 (N-H…O)GLU166 (N-H…O)GLU166	1.848 2.070 2.207 2.577
4	PEXIDARTINIB	25151352	**-3.78974**	(O…H-N)ASN142 (N-H…O)GLU166 (N-H…O)GLU166 (N-H…O)GLU166	2.275 2.251 2.236 2.123
5	SELPERCATINIB	134436906	**-3.68206**	(O-H…O)ASN142	2.048
6	ALPELISIB	56649450	-3.191136	(N-H…O)GLU166 (N-H…O)GLN189 O…H-N)GLN189 (O…H-O)ASN142	1.878 1.962 1.934 2.319
7	UPADACITINIB	58557659	-2.999962	(O…H-N)ASN142 (N-H…O)THR25	1.992 1.891
8	CAPMATINIB	25145656	-2.829649	(N-H…O)ASN119	2.239
9	AVAPRITINIB	118023034	-2.755488	(N-H…O)GLU166 (N-H…O)GLU166 (N-H…O)PHE140	2.630 1.615 2.393
10	RIPRETINIB	71584930	-2.25944	(N-H…O)SER123 (N-H…O)SER123	1.959 2.388
11	ZANUBRUTINIB	135565884	-1.865972	(N…H-N)ASN142 (O…H-N)GLN189	2.230 2.023
12	SELUMETINIB	10127622	-1.759336	(N-H…O)GLU166 (O-H…O)GLY138	1.946 2.029
13	TUCATINIB	51039094	-1.620204	(O…H-N)ASN142	2.240
14	ERDAFITINIB	67462786	2.009163	(N-H…O)GLN189 (O…H-N)GLN189 (N-H…O)02J 1 (N-H…N)02J 1	2.119 2.114 2.383 2.057

DISCUSSION

The outbreak of corona virus has become a very big challenge worldwide. Increase in the death rate grabbed the attention of global researchers to develop a cure for the deadly disease. *In silico* drug design is an effective and rapid way to identify a potential solution for the treatment. The present study aimed to predict an effective inhibitor from FDA approved anticancer drugs against corona virus. Docking studies were performed over 14 anticancer drugs against COVID-19 main protease (PDB ID: 6LU7), a key enzyme which involves in the viral replication and transcription. All the 14 compounds were docked against the target enzyme and ranked based on the Glide Score. The efficacy of the compounds were compare with the anti-viral drugs Umifenovir and Favipiravir which are used in the treatment of COVID-19 (***Costanzo et al., 2020).***

Out these 14 compounds, Entrectinib**,** Fedratinib, Pemigatinib, Pexidartinib, Selpercatinib showed better binding affinity with better glide score when compared with Umifenovir and Favipiravir.

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