Potential therapeutic agents against CoVID-19 based on molecular docking

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Abstract: The commotion caused due to the outburst of the coronavirus is in an extreme need for the development of a therapeutic agent/biomarker against the causative agent. In this study, we have studied the virtual interaction between COVID-19 protease (6LU7) and commercially available drug molecules using the Discovery Studio software suite. The docking results showed a higher affinity of the drug molecules Ara-A (vidarabine) and Ara-C (cytarabine) towards the fifth binding pocket of the protease predicted by the software. We propose that these drugs can be used as therapeutic agents/biomarker in this case.

Introduction: The end of 2019 witnessed an outbreak of a fatal infection caused by the novel coronavirus in Wuhan, China. The subsequent periods beheld the spread of the virus across the boundaries of countries and continents. As of March 3rd 95,116 confirmed cases and 3,283 deaths were reported across the world (https://infographics.channelnewsasia.com/covid-19/map.html). With the unavailability of any proven antiviral drugs against the novel coronavirus medical professionals have attempted to just supportive care for the past periods. However, researchers across the world have reported that viral restraining mechanisms can be a possible solution until the perfect drug against the virus is developed. The three dimensional structures of the viral proteins were unavailable until the recent availability of the PDB ID: 6LU7 protease in the RCSB public domain (1,2). HIV inhibitory drugs although have been found to exhibit appreciative interactions with the protease the binding energies obtained are quite high. Here, we screened a number of commercial drugs obtained from seaweeds and sponges and studied their virtual interactions with the protease. Two drugs named Ara-A (commercial name: vidarabine; which is active against *Herpes simplex* virus and *Varicella zoster* virus) and Ara-C (commercial name: cytarabine; which is used to treat acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML) and Non-Hodgkin's lymphoma) were especially analysed for their affinities towards the COVID-19 protease (3).

Method: In this study we chose 3-chymotrypsin like protease (3CL-protease)which is the main protease used to cleave polyproteins into replication-related proteins, as the target receptor. The three dimensional protein structure (PDB ID: 6LU7) was obtained from the RCSB Protein Data Bank.

Based on the literature survey we tested Indinavir, vidarabine and cytarabine for its affinity towards the 3CL-protease. We downloaded the three dimensional structures of each drug from the PubChem database in Structure Data Format (SDF) format.

The molecular docking and visualisation was performed using the DiscoveryStudio (DS) software suit (version v18.1.100.18065) (4). The protein purification, preparation and ligand preparation were performed automatically in the DS. Molecular Docking was executed for accurate docking of ligands into protein

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active sites using the Libdock module of the DS, which is a high-throughput docking algorithm that positions catalyst generated ligand conformations in the protein active site based on polar and apolar interaction sites (hotspots). A polar hotspot is preferred by a polar ligand atom and an apolar hotspot is preferred by an apolar ligand atom. Further, to identify definite residues of the receptor with the bound ligand a two dimensional diagram of docking was also performed. Default scoring function was used to score the interactions. The interaction poses were analysed manually considering the number of hydrogen bonds and libdock score. The binding energies of the selected poses were calculated subsequently.

Result: Five binding pockets or receptor cavities were predicted by the software. Table1 provides the docking scores of the two ligands in each of the five predicted binding pockets. The fifth binding pocket showed the maximum affinity with a high docking score and the least binding energies. The molecular properties of both the ligands satisfy Lipinki's thumb rule for molecular stability. Figure 1 and 2 shows the two dimensional images of the interacting residues of the target to the ligand molecules and the graphical hydrophobic surface views of Ara-A and Ara-C respectively. Further, the similarity between the SARS-CoV protease and CoVID-19 protease led us to search the active site residues of the SARS-CoV protease in the CoVID-19 protease (5,6). Interestingly, the active residues of the SARS-CoV protease were found to be present in the fifth binding pocket of the target protease indicating that the predicted receptor binding cavity could possibly be the active site of the CoVID-19 protease.

Table1. Docking Results

Docking	No. of Poses Obtained	Ligand	Index No.	H-Bond Interaction	Other Interactions	Docking Score	Binding Energy (kcal/mol)
Docking in 1st Binding Pocket.	357	Ara-A (vidarabine)	56	Asp 187, Glu 166, Gln 189	Met 165, Met 49	79.9656	-57.7295
		Ara-C (Cytarabine)	203	Met 49, Glu 166, His 164	Gln 189, Met 165, Arg 188, Asp 187, Tyr 54	86.2856	-0.1655
Docking in 2nd Binding Pocket.	536	Ara-A (vidarabine)	84	Gln 110, Glu 240, His 246	Gly 109, Pro 108	57.7599	-9.5821
		Ara-C (Cytarabine)	490	Glu 240, Gly 109, Asn 203, Gln 110	Val 202, Ile 200	62.2939	-36.9771
Docking in 3rd Binding Pocket.	0	Results zero poses.					
Docking in 4th Binding Pocket.	12	Ara-A (vidarabine)	4	Thr 304, Gln 256	Gln 306, Val 303, Val 212	80.0168	6.30443e+06
		Ara-C (Cytarabine)	5	Gln 306, Arg 217, Thr 257, Val 303	Thr 304, Gln 256, Val 212	79.4764	20.8322

Docking in 5th Binding Pocket	**534**	**Ara-A (vidarabine)**	**20**	**Thr 26, Cys 145, Asn 142, His 163, Leu 141**	**Gly 143, Glu 166, Phe 140, Ser 144**	**87.611**	**-64.0738**
		Ara-C (Cytarabine)	**407**	**Glu 166, Phe 140, His 163, His 164, Cys 145**	**Asn 142, Leu 141**	**76.3086**	**-58.4048**

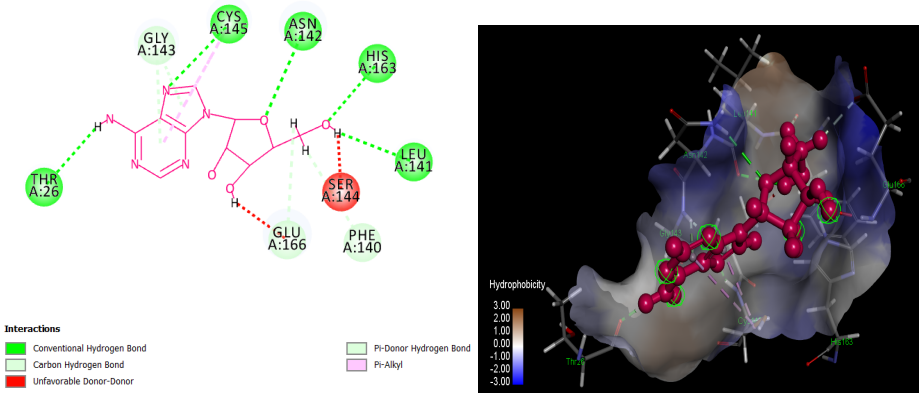

Fig.1. Docking interactions of Ara-A **(Vidarabine)** with the viral protease, two-dimensional (left) and hydrophobic surface view (right)

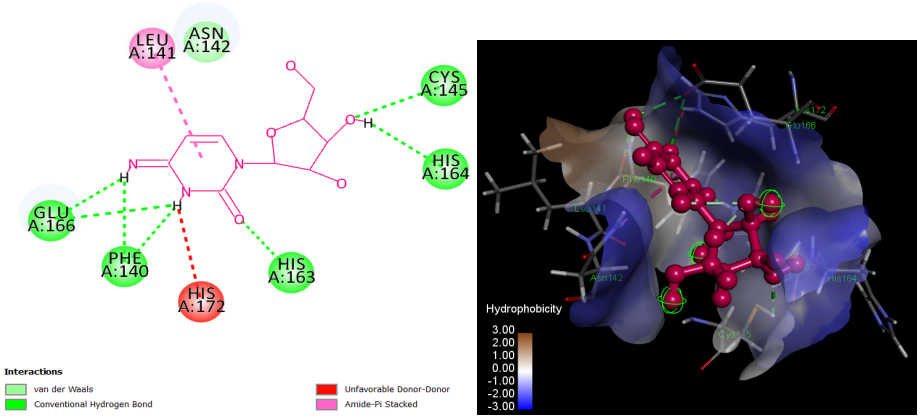

Fig.2. Docking interactions of Ara-C **(Cytarabine)** with the viral protease, two-dimensional (left) and hydrophobic surface view (right)

Finally, there may be a number of molecules showing higher affinities to the protein but due to the emergency situation arising in the world which needs to be controlled, it is preferred to choose commercially available drugs, although possibilities of many efficient drugs can be further explored in future.

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