Potential antiviral drug molecules against 2019-nCoV

Ramya Krishnan[1], Shahanas Naisam[2], Divani S, Nidhin Sreekumar[3]
OpenMind Initiative, Accubits Invent, Accubits Technologies Inc.

Purpose: Finding a drug molecule that interacts with the COVID-19 protease through virtual molecular docking analysis.

Method: A list of ligand molecules derived from seaweeds and sponges were studied for their abilities to interact with the COVID-19 protease through simulation studies using Discovery Studio Software suit.

Outcome: Two potential commercial drug molecules named Ara-A (Vidarabine) and Ara-C (Cytarabine) showed high affinities towards the target protease.

Summary: An interesting challenge was taken up by the OpenMind team of Accubits Technologies Inc., regarding the fatal disease caused by the coronavirus, which has turned out to be a vicious monster and is currently considered incurable. The spread of coronavirus has been monitored and displayed on a public platform, which shows a staggering 92,109 confirmed cases globally, as of March 3, 2020 (https://infographics.channelnewsasia.com/covid-19/map.html). The Coronavirus, as its name suggests, is a virus whose structure as a virion consists of a nucleocapsid protein, spike protein, and a membrane protein. The structures of the said proteins have been under study by different research groups around the world and the current scenario has the structure of the main protease COVID-19 (PDB ID-**6LU7**) along with an inhibitor chain is open to the public domain. The OpenMind team initiated the task of finding a ligand molecule with high affinity towards the protease. The aim was to find an interacting molecule that can either be a biomarker of the disease or a can act as a possible drug against the disease.

Since the target molecule was a viral protein, the study performed concentrated on the known antiviral molecules. Further, we chose to start with the antivirals that are produced by the sponges/corals/sea-weeds. Sponges and seaweeds have been a source of antivirals for a long time [1,2,3]. Moreover, either due to lack of the study area or other unreported reasons, we came across limited reports regarding the viral inhabitants of sponges/sea-weeds. Using these basic literature surveys as the foundation for the study, we listed a number of antivirals from these sources. We came across many antiviral molecules among which we chose two commercially available antiviral drugs named Ara-A **(Vidarabine,** CAS Number 24356-66-9 obtained from *Tethya crypta***),** which is active against herpes simplex and varicella-zoster viruses, and Ara-C (**Cytarabine,** CAS Number 147-94-4 obtained from *Tethya crypta***),** used to treat acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), and non-Hodgkin's lymphoma for our docking study. Being aware of the current state of the disease and being aware of the requirement of emergency treatment, we chose to use only commercially available drugs, that would prevent the time involved in clinical trials and the market arrival of a drug.

A virtual study of interaction of drug molecules with the protein, called docking, was performed at the Department of Computational Biology and Bioinformatics, University of Kerala, using Discovery

[1] Dr. Ramya Krishnan, Research Associate, Accubits Invent, Accubits Technologies Inc.
[2] Ms. Shahanas Naisam, Bioinformatician, Accubits Invent, Accubits Technologies Inc.
[3] Dr. Nidhin Sreekumar, Chief Research Scientist, Accubits Technologies Inc. nidhin@accubits.com

Studio (Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Discovery Studio Client v18.1.100.18065), which is a complete suite of software for simulating macromolecules and small-molecule systems.

The protein was predicted to consist of five binding pockets by the software prior to the actual docking, among which the fifth binding pocket was found to have appreciable interactions with the drug molecules. Interestingly both the drug molecules, Ara-A and Ara-C showed good binding affinities to the docked protein (PUL7) with a docking score of 87.611 and 76.3086 respectively and binding energies of -64.0738 and -58.4048 respectively. In addition, both the drug molecules are commercially available in the market and satisfy Christopher A Lipinski's rule, popularly known as the Lipinski thumb rule that determines the stability of a druggable molecule.

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**

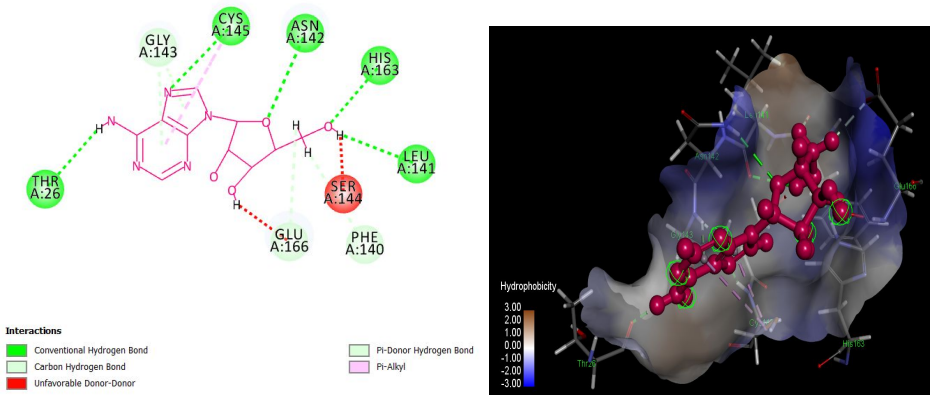

Fig.1. Docking interactions of Ara-A **(Vidarabine)** with the viral protease, two-dimensional (left) and hydrophobic surface view (right)

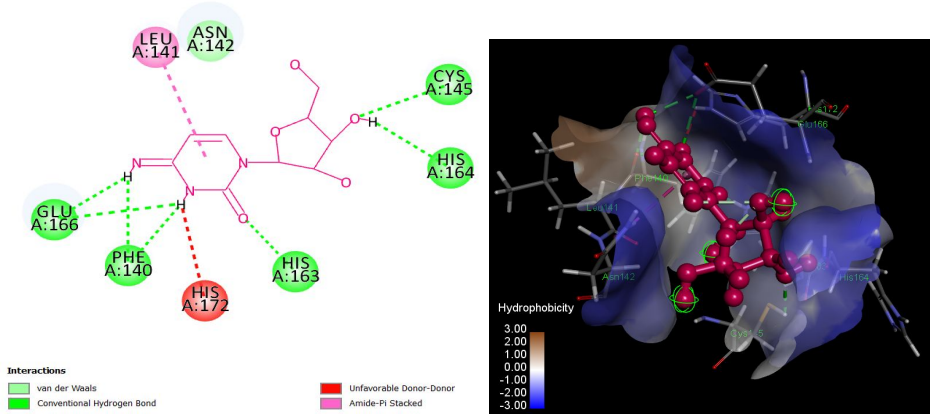

Fig.2. Docking interactions of Ara-C **(Cytarabine)** with the viral protease, two-dimensional (left) and hydrophobic surface view (right)

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.

Acknowledgement

The authors acknowledge the software access provided by Dr. Achuthsankar S Nair of the Department of Computational Biology and Bioinformatics, University of Kerala.

References

1. Yasuhara-Bell, Jarred, et al. "In Vitro evaluation of marine-microorganism extracts for anti-viral activity." Virology journal 7.1 (2010): 182.
2. Pinto, Ana Maria Viana, et al. "Marine natural seaweed products as potential antiviral drugs against bovine viral diarrhea virus." Revista Brasileira de Farmacognosia 22.4 (2012): 813-817.
3. Jia, Yan-Lai, et al. "Pestalotiolide A, a new antiviral phthalide derivative from a soft coral-derived fungus Pestalotiopsis sp." Natural Product Sciences 21.4 (2015): 227-230.
4. Dassault Systèmes BIOVIA, Discovery Studio Modeling Environment, Release 2017, San Diego: Dassault Systèmes, 2016.