Drug Docking Studies with SARS-CoV-2

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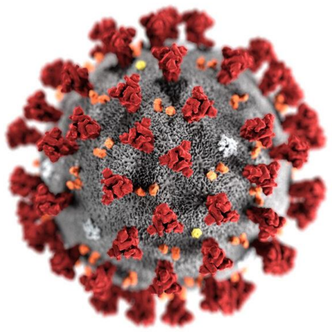
Introduction

Computer-based docking has recently moved to the forefront of drug discovery research as it allows scientists to quickly and affordably understand how small molecules bind and interact with proteins and other biological structures. This technology allows researchers to quantitatively evaluate the potential of large numbers of ligands to act as therapeutic drugs, which greatly narrows down the laboratory testing required for further studies. SARS-CoV-2, the virus responsible for the COVID-19 pandemic, emerged early in 2020 as a large global threat and stimulated the rapid response of scientists all over the world as they searched for preventative and reactive measures to hinder it.



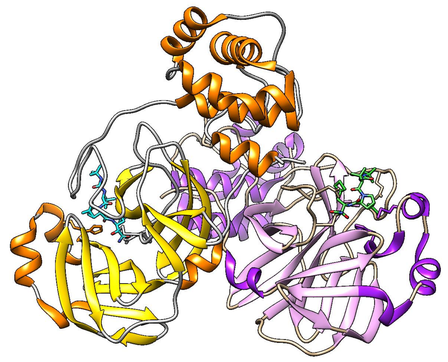
SARS-CoV-2 virus. CDC.

Transition from DOCK 6 to PyRx

This investigation into computer-aided drug design began using the UCSF DOCK 6 program, which predicts binding of small molecules using various algorithms. It quickly became apparent that DOCK 6 was not very user-friendly to chemists first getting started with molecular docking. A more accessible program called PyRx was found with the help of Dr. Muzyka. This program was much easier to download, did not require a very deep understanding of computer programming, and had a navigable interface that gave more straightforward docking results. The PyRx tutorials were easier to follow and could be accomplished in terms of hours instead of days. A couple drawbacks of PyRx is that it is less refined and accurate than DOCK, but the results are satisfactory for the scope of our research.

SARS-CoV-2 Main Protease

SARS-CoV-2, a deadly coronavirus, works under the same functionality as most other viruses. Upon entry into the body, a SARS-CoV-2 virus binds to an ACE2 receptor on the surface of cells mainly in the lungs using a spike protein. Upon entry into the cell, the viral capsid hijacks host cell ribosomes to translate the virus's RNA into viral proteins, allowing for replication of the virus and its subsequent spread throughout the body. Sixteen non-structural proteins are synthesized from the virus via host cell machinery to assist in the seven-step process of viral replication, making them attractive targets for inhibition. NSP5, also known as the main protease, is responsible for cleaving much of the amino acid sequence synthesized in the host cell into individual non-structural proteins crucial for replication. The main protease has a cysteine-histidine residue in its active site and can cleave glutamine-serine, glutamine-alanine, and glutamine-glycine peptide bonds. If the main protease can be targeted in treatment, then replication of the SARS-CoV-2 virus is massively disrupted, making it a focal point of drug design.



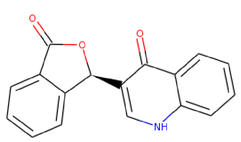
Both subunits of main protease in complex with boceprevir.
PDB: 7BRP

Preliminary Docking Results

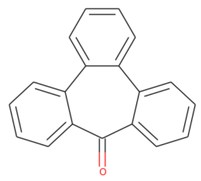
Ideal docking results for viable drug targets will be at binding affinities of -9 and lower. Because of the main protease's ability to cleave Q-S/A/G links, peptide analogs of similar structure are predicted to be suitable ligands. Thus far, the ligands that have been docked in PyRx with the main protease have only yielded binding affinities as low as -7.1. However, computations done by Dr. Toth's students are in progress that have already shown binding affinities as low as -9.5.

LIGAND PDB	BINDING AFFINITY (kcal/mol)
23H	-7.0
959	-5.4
APR	-6.8
G85	-7.1
SAH	-6.7
WR1	-6.2
ZU3	-7.1
ZU5	-6.5

Binding affinities of the most favorable conformation of various ligands with the main protease.



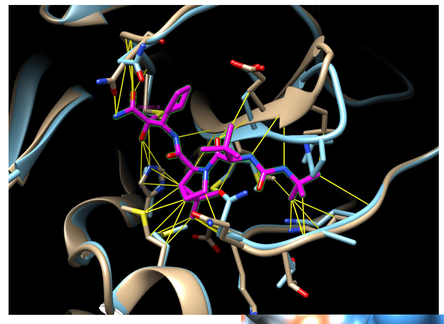
Binding affinity: -9.4 kcal/mol
(ZINC5545321)



Binding affinity: -9.5 kcal/mol
(ZINC5948917)

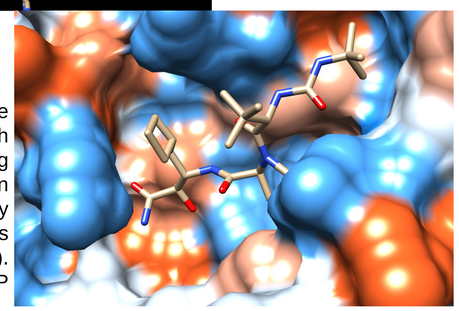
Visualizing Docking Results

Although PyRx provides valuable quantitative binding results, its imaging is not very accessible nor digestible. Chimera can be used to visualize the docking results from PyRx. The qualitative binding site interactions of the main protease with a ligand can be clearly highlighted with colorful modifications and affinity labeling that researchers can adjust to their liking.



LEFT: Superposition of main protease in complex with boceprevir (tan) and unbound main protease (blue), showing residue interactions in yellow between ligand (pink) and main protease (tan).
PDB: 7BRP, 7BRO

RIGHT: Main protease in complex with boceprevir. Binding site surface of main protease is labeled by hydrophobicity (blue is polar, red is nonpolar).
PDB: 7BRP



Conclusions and Future Work

Computer-based drug docking with the SARS-CoV-2 main protease shows promise for identification of viable small molecules for further study as anti-viral treatments.

Future plans include:

- Analyzing additional results from higher-level docking calculations.
- Identifying other potential drug targets for SARS-CoV-2 inhibition for further docking studies.

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