A NOVEL COMPUTATIONALLY DESIGNED TOOL TO TREAT THE COVID -19 PANDEMIC

Chikoo Cherry Abraham Cherian, Ph.D, Karunya Institute of technology and Sciences, Tamil Nadu, India.

INTRODUCTION

The Coronavirus pandemic that is plaguing the world for the past few months since December 2019 has rendered panic and worldwide fear among all nationalities. Originating from Wuhan , Hubei, China, the disease shows symptoms similar to that of the viral pnuemoniae [1]. The race to find a novel drug to treat the disease has been taxing and challenging.

Drug repurposing is one approach that researchers have implemented to find a cure. This has led to the prescription of Chloroquine - the drug used to treat malaria, lupus and rheumatoid arthritis. In an attempt to self-medicate, a Phoenix based coronavirus affected patient has lost his life and his wife is under critical care . It was reported that within thirty minutes of ingestion, the couple experienced the need to be admitted to the Banner Health Hospital. In this case because of other reported cases of side effects caused by Chloroquine in treating the disease, derivatives of Chloroquine was administered [2].

In silico biology refers to the experiments that is needed to be performed in a computer which can aid in the drug discovery and reduce the time and need for expensive lab work and clinical trials. Computational tools aided in the drug design of a novel molecule that acted as an inhibitor of the coronavirus protein structure that was deposited in the Protein Data Bank having the accession number 6M03.

This article aims to highlight the efficacy of the novel designed molecule against the virulent coronavirus protein structure. It was done to enumerate and highlight the identified small molecule with the aid of computer-centric research that is a relatively new paradigm. We utilized an ensemble of methods that utilizes molecular docking techniques. The docking method fits a ligand into the binding site by combining and optimizing variable like steric, hydrophobic and also estimating the free energy of binding. In addition to this, the physicochemical properties were utilized to define the drug-like properties of these compounds. The statistics were compared to that of chloroquine, where it did not bind and showed toxic parameters that may have contributed to the side effects rendered by the repurposed drug.

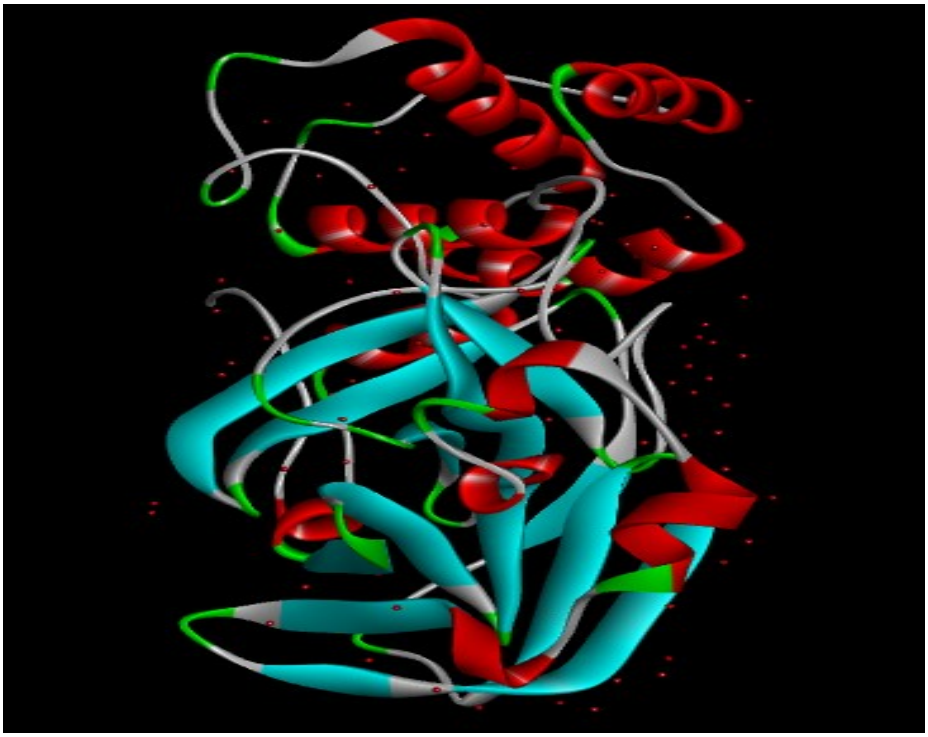
MATERIALS AND METHODS

SeeSAR is a software tool for interactive, visual compound prioritization as well as compound evolution. Structure-based design work ideally supports a multi-parameter optimization to maximize the likelihood of success, rather than affinity alone [3].

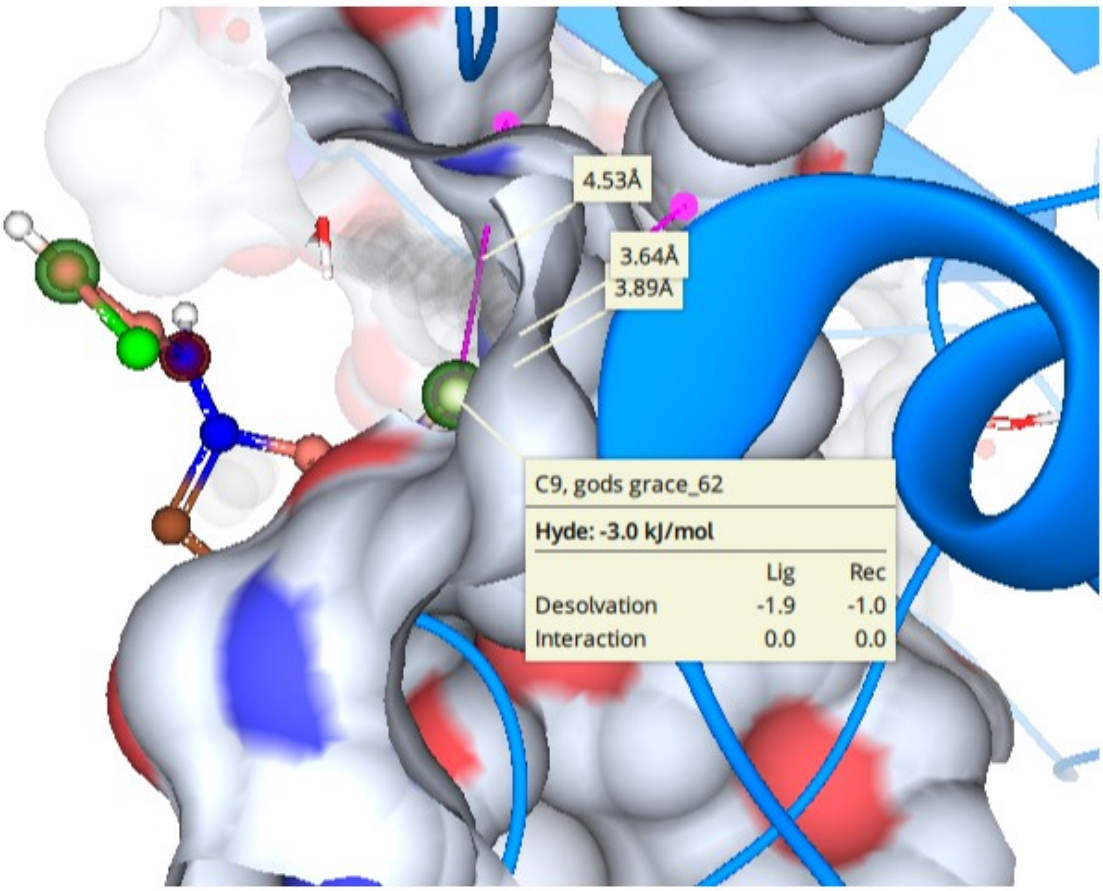
The experiment required the target coronaviral protein [4] that was retrieved from the Protein Data Bank [5] for the analysis. The parameters used for this study involved log D, a parameter used to predict the logarithm of octanol/water partition coefficient for ionised compounds at a fixed pH of 7.4. The Intrinsic Aqueous Solubility (log S) predicts the logarithm of the Intrinsic aqueous solubility. The Blood-Brain Barrier Penetration was used as a parameter for prediction. The hERG pIC50 values predicted the inhibition of hERG K+ channels expressed in mammalian cells. The 2D6 affinity which gave a pKi value between 5 and 6. The Human Intestinal Absorption (HIA) classification predicted if the compound was absorbed. The Plasma Protein Binding predicted a classification for the compound if it was bound or not.

RESULTS AND DISCUSSION

The crystal structure of COVID-19 main protease in apo form structure deposited in the Protein Data Bank was used for the analysis (Figure1).



The binding of the novel drug molecule to the protein structure has marked a template for its active site binding and the inhibition of the activity contributed by the amino acid residues in the surrounding region. A couple of ligands were taken for consideration to bind and inhibit the activity of the structure. This included even repurposing well known counter-the-top drugs including chloroquine. None of them showed any binding affinity to the protein structure. A couple of well known natural compounds were even taken into consideration for the binding. This too proved to be futile. A compound that was designed computationally was used to bind to the structure. It bound to the structure (Figure 2) as well as showed the pharmacokinetic properties of a good drug, including the Lipinski Rule of Five.



The first factor that need to be taken into consideration is LogP, that describes the Lipophilicity of a drug molecule with respect to the ionic states present at key biological pH values [6]. Lipophilicity not only impacts solubility but also influences permeability; potency; selectivity; absorption, distribution, metabolism, and excretion (ADME) properties; and toxicity. Lipophilicity values are usually measured for drug candidates to support structure-activity relationships, absorption and tissue distribution prediction, physiologically based pharmacokinetic modeling, preformulation, formulation, and environmental assessment. High lipophilicity (logP>5) often contributes to high metabolic turnover, low solubility, and poor oral absorption [7]. Recent studies have shown statistically significant improvements in safety outcomes from early in vivo safety studies when compounds have logP<3 [8]. The novel molecule designed had a Log P of -7.2906 which is much lesser than Chloroquine (4.8106).

The 2C9pki values while a classification model is present in the package for 2D6 (low (pKi < 5), medium (5 < pKi < 6), high (6 < pKi < 7) and very high (pKi > 7)). In the order to facilitate the analysis, we categorized the predicted 2C9 following the approach used for 2D6. These estimations suggest that iPPIs and nuclear receptor compounds tend to inhibit both these isoforms [9]. It is 4.15684 for the novel molecule which makes it fall under the “low” category, whereas chloroquine had 4.5282, where it comes close to the “medium” category.

Increasing lipophilicity can increase metabolic and efflux clearance. Therefore, if lipophilicity is increased for BBB permeability, effects on clearance should be checked [7]. In this context, the Log D value is higher for Chloroquine, rendering a BBB log([brain]:[blood]) of -0.18987 for the novel molecule and 0.236058 for chloroquine.

Prediction of human intestinal absorption (HIA) is a major goal in the development of oral drugs [10]. The Human Intestinal Absorption (HIA) classification predicted a '-' for the compound which clearly indicated that > 30 percent of the compound was absorbed, but it indicated a ‘+’ for chloroquine.

The Intrinsic Aqueous Solubility (log S) predicted the logarithm of the Intrinsic aqueous solubility where, it was higher (4.74705) than chloroquine (2.43421).The hERG pIC50 values predicted the inhibition of hERG K+ channels expressed in mammalian cells. It was lesser (4.06831) than chloroquine (6.20479). The Plasma Protein Binding predicted a classification of 'low' for the compound because it was <90% bound.

These critical factors determine the efficiency of the new proposed drug and the reasons it can be a substitute to chloroquine.

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