Original Research

In silico studies of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives as potential inhibitors against main protease covid-19 enzyme

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Abstract

The 2019 coronavirus (COVID-19) pandemic is spreading worldwide, with a spectacular increase in death missing any effective therapeutic treatment up to now. Molecular docking is a recognized computational tool to assist in early drug discovery and development. Molecular docking analysis was carried out using 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base conjugates with SARS-CoV-2 protease enzyme and COVID-19 main protease in apo form (6M03). The compounds with the best normalized docking scores to protease enzyme (6LU7) were ARG3 (-8.1 kcal/mole), ARG7 (-8.1 kcal/mole) and ARG6 (-8.0 kcal/mole). The best docking ligands for main protease in apo form (6M03) were ARG7 (-8.7 kcal/mole), ARG6 (-8.6 kcal/mole) and ARG3 (-8.4 kcal/mole). The structural similarity between these conjugates inspired us to perform *in silico* studies to check their possible binding interactions with essential SARS-CoV-2 proteins. These studies provide insight into the potential binding between Schiff base derivatives and SARS-CoV-2 proteins to provide an insight for finding an effective therapy. Finally, ADMET calculations were performed for the Schiff base compounds to predict their pharmacokinetic profiles.

Keywords: *Coronavirus, COVID-19, molecular docking, protease covid-19 enzyme, Schiff base*

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Introduction

The outbreak of Coronavirus SARS-Cov-2 disease (COVID-19) in Wuhan (China) in December, 2019 and its worldwide spread has led in some cases to serious disease symptoms finally leading to several cases of deaths [1, 2]. During the year 2020, the disease has affected almost all countries on the globe. The majority of people infected with the COVID-19 virus have mild to medium respiratory symptoms and recover mostly without any treatment [3-5]. Elderly people and people with chronic medical conditions such as diabetes, cardiovascular diseases, chronic respiratory diseases, or cancer develop more severe symptoms [6, 7]. The virus produces a S-glycoprotein on its surface that is responsible for its attachment to a host of receptors, named angiotensin-converting enzyme-2 (ACE2), initiating cell entry. The sequencing of the SARS-CoV-2 genome showed that it encodes for 16-17 non-structural proteins such as protease enzymes and ACE2 cellular receptors using the viral spike proteins [8]. The inhibition of proteases enzymes which are essential in both maturation and infectivity of the virus can help in protection from the SARS-CoV-2 viruses. In addition, RNA-dependent RNA polymerase (RdRp) allows the viral genome to be copied into the new RNA strand using the host cell's machinery and this could be another target for fighting the SARS-CoV-2 viruses [9, 10]. Further, they could decrease the risk of drug-resistance produced

by mutation. Following the protease inhibition approach two standard protease inhibitors were used as leading compounds including Lopinavir and N3 inhibitors recognized of being able to inhibit SARS-CoV main protease [11]. Thus, it has been reported that the SARS-CoV main protease has 96.1% homology with the COVID-19 main protease and therefore may be used as a homologous target for the screening of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives that could inhibit the proliferation and replication of COVID-19 [12-15]. The 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives are Schiff bases recognized for their therapeutic value as they were reported to have anti-inflammatory, analgesic, antiviral, antitumor, antifungal and antibacterial properties [16-21]. Molecular modeling is a recognized computational tool to aid early drug discovery and development. It is used to generate ideas of a compounds or macromolecules 3D conformation, protein–ligand interactions, and allows forecasts about biological activities. The integration of molecular modeling in drug or vaccine design can help in early drug or vaccine discoveries [22-24]. The main aim of this study is to perform molecular modeling studies on 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives against two essential target proteins of the SARS-CoV-2 virus and predict their pharmacokinetic properties for rapid drug discovery.

Materials and Methods

Molecular docking

In this paper, the docking studies of the designed (not synthesized) 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives have been carried out to predict the most possible type of interaction, the binding affinities and the orientations of the docked ligands at the active site of the target proteins. The starting geometry of the 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base was constructed using chem3D Ultra software (version 8.0, Cambridge soft Com., USA). The optimized geometry of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives with the lowest energy was used for molecular dockings. The crystal structure of COVID-19 main protease complex with the inhibitor N3 (6LU7) was downloaded from the Protein Data Bank http://www.rcsb.org/structure/6LU7 and COVID-19 and the main protease in the apo form (6M03) was downloaded from the Protein Data Bank http://www.rcsb.org/structure/6m03. Molecular dockings of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives with 6LU7 and 6M03 was accomplished by Auto Dock 4.2 software from the Scripps Research Institute (TSRI) (http://autodock.scripps.edu/). Firstly, polar hydrogen atoms were added into protein molecules. Then, partial atomic charges of the protease enzymes and 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives molecules were calculated using Kollman methods [25]. In the process of molecular docking the grid maps of dimensions: (60Å X 60Å X 60Å) and (36.8Å X 64.6Å X 60Å) for 6LU7 and 6M03, respectively, with a grid-point spacing of 0.376Å and the grid boxes centered. The number of genetic algorithm runs and the number of evaluations were set to 100. All other parameters were default settings. Cluster analysis was performed based on docking results by using a root mean square (RMS) tolerance of 2.0Å, dependent on the binding free energy. Lastly, the dominating configuration of the binding complex of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives and protease enzymes fragments with minimum energy of binding were determined which relied strongly on the information of 3D-structures of the protease binding site and ultimately generated a series of protease-binding complexes.

In silico Toxicity Assessment of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives

The *in silico* toxicity assessment of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives was made with an online tool called ProTox-II: a webserver for the prediction of toxicity of chemicals (http://*tox.charite.de/protox_II*/) [26]. The drug-likeness for 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives was evaluated through Lipinski Rule of Five using the server called SwissADME provided in the web link below [27].

Results and Discussion

Molecular docking analysis

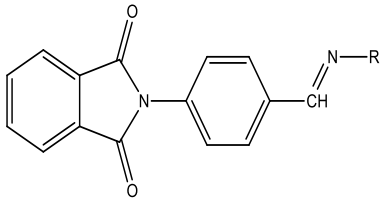
Computer-aided drug designing, especially molecular docking methods have been found to be an efficient technique to screen a potential drug candidate against a specific disease. Molecular docking study provides an insight into the effectiveness of binding of ligands against the studied receptor protein. Recent studies have shown that the main protease of SARS-CoV-2 have been found to consist of three domains *viz*: domain I (residues 8-101), domain II (residues 102–184) and domain III

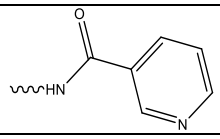
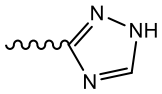
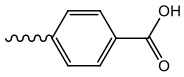
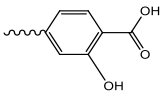
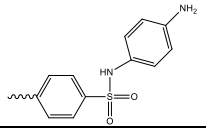
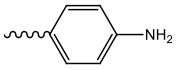
(residues 201-303) and as similar to other coronaviruses, SARS-CoV-2 Mpro also consist of a Cys145-His41 catalytic dyad located in a cleft between domain I and domain II [28, 29]. **Table 1** shows the binding energies of Lopinavir, N3 (as standards), 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives, and protease enzymes (6LU7 and 6M03) obtained by the molecular docking strategy. Molecular dockings of the 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives with protease enzymes (6LU7 and 6M03) were performed using Auto Dock 4.2 to obtain information about the interaction forces between 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives and protease enzymes (6LU7 and 6M03). 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives and protease enzymes (6LU7 and 6M03) were kept as flexible molecules and were docked into seven forms of rigid protease enzymes (6LU7 and 6M03) to obtain the preferential binding site to 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives on protease enzymes (6LU7 and 6M03). The molecular docking results are shown in Table 1. The modeling studies indicate *van der Waals*, hydrogen bonding (Table 1) and electrostatic interactions between 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives with protease enzymes (6LU7 and 6M03). The contribution of *van der Waals* and hydrogen bonding interaction is much greater than that of the electrostatic interaction because the sum of *van der Waals* energy, hydrogen bonding energy and desolvation free energy is larger than the electrostatic energy, [30, 31]. The 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives, and protease enzymes (6LU7 and 6M03) interactions are shown in **Figure 1**. 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives provide higher binding energy (-7.0 to -8.7 kcal/mol) compared to standard 6LU7 and 6M03 (-7.0 to -7.9 kcal/mol) **Table 1**. **Figure 1** indicates four hydrogen bonds between ARG6 and 6LU7. In addition, ARG6 showed good docking interaction of -8.0 kcal/mol with the 6LU7 binding site (LYS5, THR199 and LEU287) (**Figure 1**). Compound ARG6 has the highest binding energy of the series with both enzymes as shown in **Table 1**. This compound has an extra N-(4-aminophenyl)-4-methylbenzenesulfonamide moiety attached to the 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione analogue of the Schiff`s base derivative with a log P value of 4.12 indicating the importance of the lipophilicity for the interaction with the active site. The interaction of similar Schiff's base *ortho*-phenylenediamine derivatives with the protease binding site of the enzyme is essential for effective inhibition as previously reported [32-35]. Therefore, 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione derivatives may be considered to be effective as protease inhibitor. It has been reported that Schiff bases of N-substituted-2-quinolonylacetohydrazides have a good activity towards SARS-CoV-2 and the molecular docking calculations showed that the majority of the tested compounds possessed good binding affinity to the SARS-CoV-2 main protease (Mpro) comparable to remdesivir [36]. It has been reported also that six novel imidazole anchored azo-imidazole derivatives have a good inhibitory effect against the main protease (6LU7) of coronavirus (COVID-19) using molecular docking studies. The binding energy (ΔG) values of the six ligands against the protein 6LU7 have found to be -7.7 Kcal/mole (L1), -7.4 Kcal/mole (L2), -6.7 Kcal/mole (L3), -7.9 Kcal/mole (L4), -8.1 Kcal/mole (L5) and -7.9 Kcal/mole (L6) which were similar to our compounds. Pharmacokinetic properties (ADME) of the ligands (L1-L6) have also been studied and the results have revealed that the ligands (L1-L6) could act as a potential drug candidate [37]. The obtained results using computational drug repurposing is an efficient way to find novel applications for already known drugs [38]. Molecular docking and binding free energy calculations for 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives can be used to forecast drug-target interactions and binding affinity. The appearance of resistance to existing antiviral drugs or vaccines is a major challenge in antiviral drug development. The drug repurposing technique allows finding novel antiviral agents within a short period in order to overcome the challenges in antiviral therapy. Computational drug repurposing has previously been used to recognize drug candidates for viral infectious diseases like ZIKA, Ebola, influenza and dengue infections. These methods were also utilized to recognize possible drugs against MERS-CoV and SARS-CoV [39, 40] and following the COVID-19 outbreak, computational repurposing has been and are used for COVID-19 treatment.

In silico toxicity assessment of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives

2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives were evaluated for drug-likeness and toxicity. Examination of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives **for** drug-likeness was performed by computational prediction of ADME-Tox properties (adsorption, distribution, metabolism, excretion, and toxicity). All 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives were found to be non-carcinogenic and acceptable as drugs [41, 42].

Table 1: Various energies in the binding process of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives, N3 and Lopinavir with COVID-19 protease enzymes (6LU7, 6M03) obtained from molecular docking. The unit of all energies (ΔG) is kcal/mol.



Comp	(R)=substituent	M.Wt	Log P Calculated	Hydrogen bonds**		Binding energy (ΔG) kcal/mol	
				donors	acceptors	6LU7	6M03
Ref comp.	**N3 Inhibitor**	**628.8**	**5.92**	**4**	**5**	**-7.9**	**-7.8**
Ref comp.	**Lopinavir**	**680.79**	**4.37**	**6**	**9**	**-7.6**	**-7.0**
ARG1		370.36g/mol	2.64	5	1	**-7.9**	**-7.8**
ARG2		317.30g/mol	2.68	5	1	**-7.6**	**-7.0**
ARG3		265.27g/mol	2.14	3	1	-8.1	-8.4
ARG4		370.10g/mol	4.08	5	1	-7.6	-8.3
ARG5		386.09g/mol	3.69	6	2	-7.0	-7.3
ARG6		496.54 g/mol	4.12	6	1	-8.0	-8.6
ARG7		341.36 g/mol	3.72	3	1	-8.1	-8.7

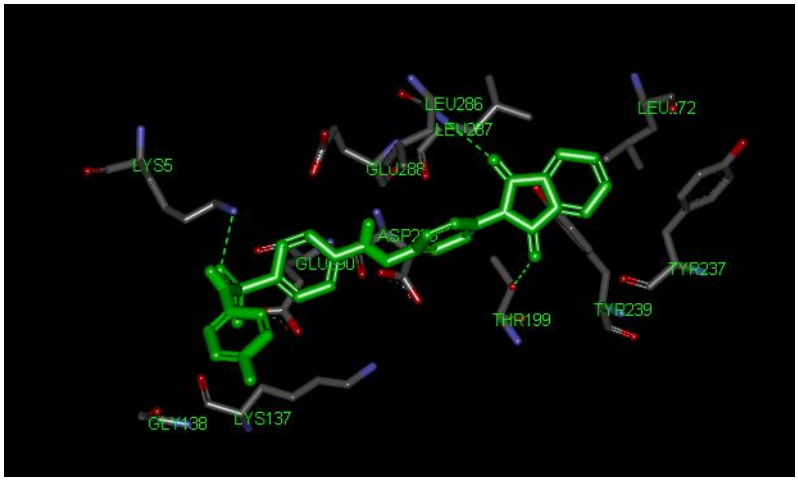


Figure 1: Interaction model between ARG6 with COVID-19 main protease (6LU7) active site. ARG6 green colour. Hydrogen bonds green broken line.

In addition, all 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives were found to follow Lipinski 's Rule of five for drug likeness with molecular mass less than 500 daltons, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, with Log P scores not exceeding 5, and molar refractivity 40-130 [27, 43]. The limitation of this study is the cytotoxicity assay, which still needs to be an essential part of evaluating the safety of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives because it affords direct information at the cellular level which may be significant in assessing the true toxicity of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives.

Conclusion

Designing efficient small-molecule therapeutics promises to be a most interesting therapeutic way to stem the tide of the COVID-19 pandemic. Consequently, a series of 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives designed as protease inhibitors were *in silico* examined for their ability to stop SARS-CoV-2 viral infection through some mechanisms. Docking studies results indicated that 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives may inhibit the protease enzymes. ADMET properties were calculated and showed satisfactory pharmacokinetic and toxicological properties. Therefore, combining the docking results, ADMET predictions and the biological activity of the studied 2-(4-(aminomethyl)phenyl)isoindoline-1,3-dione Schiff base derivatives can be considered as COVID-19 proteases inhibitors. We suggest that these compounds shall be further studied for suitable therapeutic treatment of COVID-19.

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Conflict of Interest

All authors declare no conflict of interest.

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