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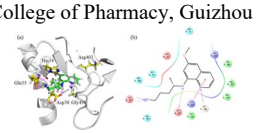
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RESEARCH ARTICLE

Title: The identification of potential inhibitors of SARS-CoV-2 spike protein by virtual screening FDA-approved compound library

Zhujia Ren, Derong Zeng, Peiqing Wang, Rong Wang, Binqing Zhou, Yan Zhang*

[1]College of Pharmacy, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China.



Abstract: Coronavirus disease 2019 (COVID-19) has an unprecedented global health crisis and economic disruptive impact, which is initiated by the spike protein of severe acute respiratory syndrome coronavirus (SARS-COV-2) binding to the angiotensin-converting enzyme 2 (ACE2) receptor of human cells. To identify potential inhibitors of SARS-CoV-2 spike protein, molecular docking-based virtual screening FDA-approved compound library was performed. Primaquine has more favorable docking scores than remdesivir, which are -8.910 and -5.725 kcal/mol, respectively. Primaquine formes hydrogen bonds with Glu35, Asp38, and Gly496 and cation-π interactions with Lys353, which contribute to the antiviral activity of primaquine. The study provides a valuable basis for the development of anti-novel coronavirus drugs.

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*Address correspondence to this author at the College of Pharmacy, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, China. Email: zhangyan0003@gzy.edu.cn

1. Introduction

T Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus (SARS-COV-2), has become the deadliest respiratory disease after it was first detected in December 2019 in Wuhan, China[1]. Because SARS-COV-2 can be transmitted by aerosols, close contact, respiratory droplets, and faecal-oral routes, it greatly affects the global economy, society, healthcare, energy, and environment[2-8]. As of 15 September 2023, there are approximately 690 million confirmed cases globally, and more than 6.9 million deaths have occurred. Typically, patients will experience fever, cough, muscle aches, sore throat and diarrhoea, while severe patients may experience respiratory failure and organ failure[9-11]. The severity of COVID-19 infection is influenced by the virulence of the SARS-COV-2 variant and the host's immune response. The National Institutes of Health (NIH) has established a disease classification system for the degree of COVID-19 infection, with criteria for asymptomatic, mild, moderate, severe, and critical. These categories are not mutually exclusive, and patients often progress from one category to the other over the course of their illness[9]. SARS-CoV-2 encodes four structural proteins: synapsid (S), envelope (E), membrane (M), and nucleocapsid (N)[12]. The N protein is responsible for binding to the viral RNA, while the S, E, and M proteins form the envelope[13]. The new coronavirus infects host cells by S protein binding to the angiotensin-converting enzyme 2 (ACE2) receptor of human cells[14,15]. Thus, the S protein becomes the most promising target for developing drug and vaccine against SARS-CoV-2.

At present, in order to curb the battle against COVID-19, many researchers at home and abroad are actively researching and developing effective medicines and vaccines. However, the long period, high cost, adverse reactions and after-effects of the disease have made the research and development process difficult [16,17]. It is advantageous to use already marketed drugs to find potentially active compounds against neocoronaviruses. Computer-aided drug design (CADD) is a technology that uses computational methods to discover and develop drugs and active molecules with phase-specific properties. The one of main contributor to CADD is virtual screening (VS) based on molecular docking [18]. CADD has greatly facilitated drug development in recent years, not only providing an accelerated pathway to find potential compounds, but also saving time, money and labour during the experimental process [19-21].

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In the study, FDA-approved compound library is performed to screen potentially active compounds based on the S protein of SARS-CoV-2.

2. Materials and methods

2.1 Structure preparation of ligands

3480 FDA-approved compounds from ZINC database were used to screen potential molecules [22]. Small molecules were prepared using Schrodinger's LigPrep module of the Schrödinger program [23], which includes transforming the three-dimensional structure of small molecule, preserving the original chirality of small molecule, adding hydrogen atoms, and minimization of the structure.

2.2 Structure preparation of the S protein

The crystal structure of SARS-CoV-2 S protein was downloaded from the Protein Data Bank (PDB ID: 6M17). The S protein was treated using the Protein Preparation Wizard module, including the addition of missing side chains and loops, assigning protonation states and adding hydrogen atoms. The OPLS-2005 force field was selected to minimize the protein.

2.3 Grid generation

The receptor grids of the S protein were defined by key residues including Tyr449, Gly496, Gln498, Pro499, Thr500, Asn501, Gly502, Val503, and Tyr505 (Figure 1). The grids were then generated using the Receptor Grid Generation module.

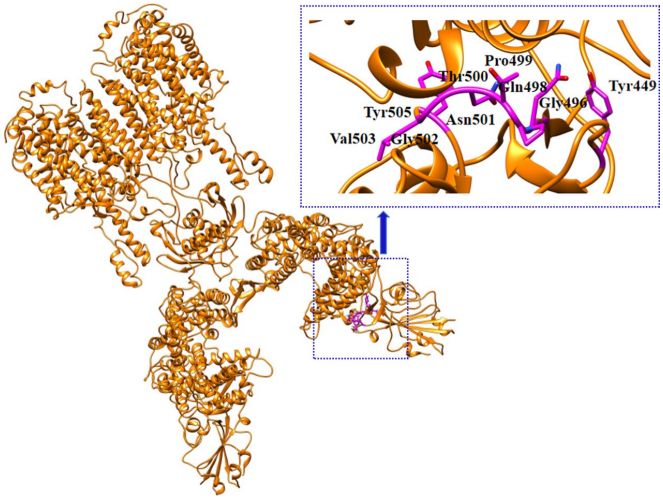


Fig. (1). Crystal structure of the spike protein of SARS-CoV-2, and the key residues defining receptor grids of the protein.

2.4 Molecular docking-based virtual screening

Virtual screening of the S protein was carried out using virtual screening workflow. The compounds were without reactive functional groups and obeyed Lipinski's Rule of 5. After that, the obtained compounds were performed to further evaluate their binding affinity between the S protein and molecules by using Glide (high throughput virtual screening, HTVS), (standard precision, SP), and (extra precision, XP).

2.5 Cluster analysis

The filtered compounds were clustered into 5 classes by Canvas. Finally, combining the results of docking scoring, and clustering analysis, some candidate compounds were selected for further structural analysis.

3. Results and discussion

3.1 Molecular docking of remdesivir

Remdesivir is an antiviral drug authorized to treat mild-to-moderate COVID-19[24]. Therefore, the molecular docking result of remdesivir and S protein was chosen as a reference and the docking scores was -5.725 kcal/mol. Remdesivir has the hydrophobic interactions with Leu45, Val445, and Val503 of S protein (Figure 2a). Additionally, remdesivir forms the hydrogen bonds with Asn49 and Asn330 of S protein (Figure 2b).

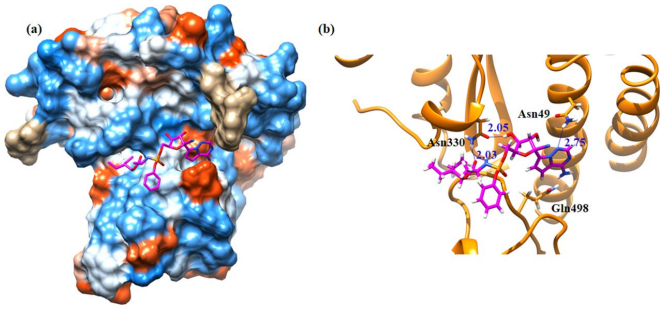


Fig. (2). Interaction mode of remdesivir with the S protein (a-b). The surface ranging from orange–red for the most hydrophobic to dodger blue for the most polar residues, with white in between.

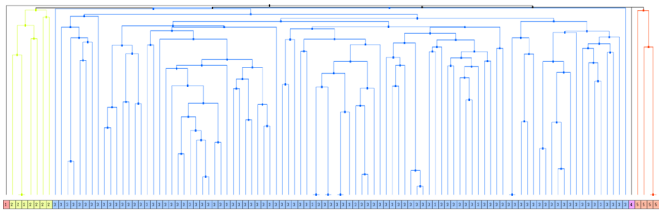
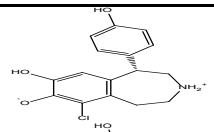
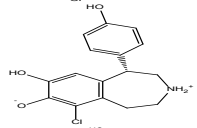
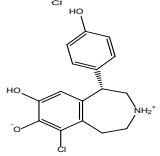
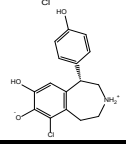


Fig. (3). Cluster analysis of compounds screened from FDA-approved compound library.

3.2 Screening of FDA-approved compound library

Table 1. The docking scores of candidate compounds binding with the S protein.

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Chemical structures	Compounds	Docking scores
	primaquine	-8.910
	Midodrine	-7.761
	Phenylephrine	-6.739
	Suprofen	-6.524

107 compounds were finally obtained using HTVS, SP and XP, and performed cluster analysis (Figure 3). These compounds were classified into 5 categories and representative compounds were selected by combining docking scores and the interactions. Most of the compounds obtained were concentrated in class 3, with very few compounds in other classes. Therefore, several compounds with high docking scores in class 3 were selected to further analysis (Table 1).

The compounds with docking scores $\leqslant -6.5$ kcal/mol are primaquine[25], midodrine, phenylephrine, and suprofen. Primaquine has the most favorable docking score, which is a potent antimalaria agent. The side chain of primaquine with Glu35, Asp38, and Gly496 formes hydrogen bonds (Figure 4). In addition, primaquine is involved in cation-π interactions with Lys353. These interactions contribute to the antiviral activity of primaquine.The important and main findings of the study should come first in the Results Section. The tables, figures and references should be given in sequence to emphasize the important information or observations related to the research. The repetition of data in tables and figures should be avoided. Results should be precise.

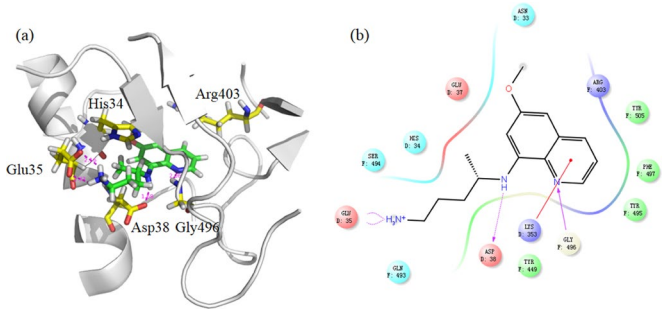


Fig. (4). Interaction mode of primaquine with the S protein (a-b).

4. Conclusion

Based on the S protein of SARS-CoV-2, primaquine is identified by virtual screening of FDA-approved compound library, which has more favorable docking scores than remdesivir. Primaquine formes hydrogen bonds with Glu35, Asp38, and Gly496 and cation-π interactions with Lys353, which contribute to the antiviral activity of primaquine. The study provides a valuable basis for the development of anti-novel coronavirus drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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