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In silico identification of a new potential drug-binding pocket on the surface of the receptor-binding domain of the SARS-CoV-2 S-glycoprotein

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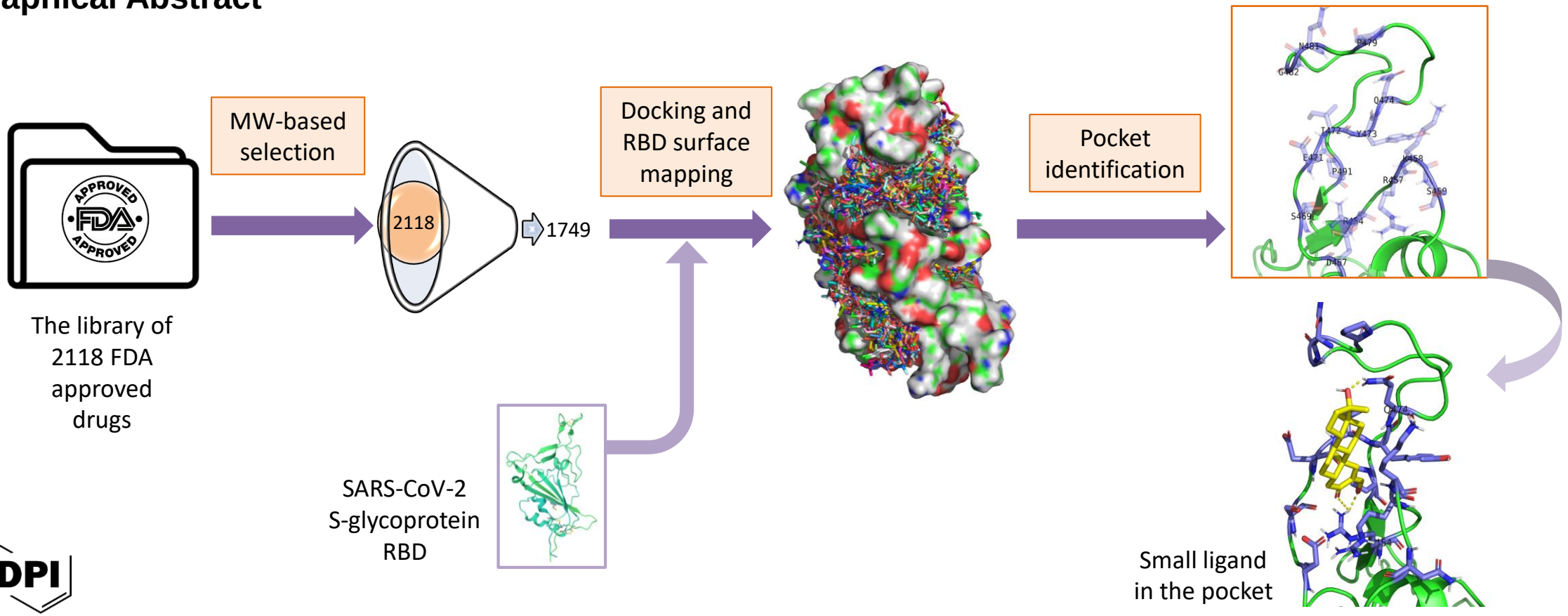
Graphical Abstract



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Abstract:
SARS-CoV-2 is an emerging pathogen that caused the largest pandemic in modern history in 2020-2023. The surface S-glycoprotein, namely its RBD, significantly determines the pathogenesis of this virus: it allows SARS-CoV-2 to target human cells and ensures its internalization. Thus, the search for RBD inhibitors is currently considered a promising strategy for the drug development against COVID-19. In this work, we identified a new pocket on the RBD surface that could potentially bind small drug-like ligands. The FDA-approved drug compound library obtained from e-Drug3D was used as a source of drug-like chemical structures. The compounds were initially filtered by molecular weight (100-500 Da) using the Open Babel GUI. This allowed to reduce the size of the library from 2,118 to 1,749 compounds. Next, all filtered structures were docked to the RBD (PDB ID: 7T9L) using AutoDock Vina 1.1.2. The docking area was the entire RBD. **Results and conclusions:** We obtained a map of the uneven placement of ligands with different affinities to the target. The pocket formed by amino acids R454, R457, K458, S459, D467, S469, E471, I472, Y473, Q474, P479, N481, G482 and P491 was identified close to the functionally important ACE2-binding site of the RBD. It was able to interact with 128 ligands with the best estimated affinity of -7.8 kcal/mol for Oxymetholone. The latter interacted with the pocket through its hydroxyl and keto groups.

Keywords: COVID-19; drug development; pocket; virtual screening; FDA.

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Introduction

- Emergent viruses have been the cause of epidemics and pandemics throughout human history. We've recently witnessed the largest pandemic of the 21st century, caused by a previously unknown member of the Coronaviridae family, now called SARS-CoV-2. Up until the official lifting of its pandemic status on May 5, 2023, this virus had caused more than seven million confirmed deaths. At the same time, attempts to combat the spread of SARS-CoV-2 through strong quarantine measures have led to significant economic losses that have negatively affected the global economic system.
- The S-glycoprotein is the main structural and functional unit that ensures the recognition of the host cell by SARS-CoV-2 and its entry into the cytoplasm. Thus, disruption of the S-glycoprotein receptor-binding domain (RBD) interaction with hACE2 can prevent SARS-CoV-2 from being recognized by the target cell and stop its spread.
- The first step in any structure-guided drug design process is to examine the target macromolecule for the presence of pockets suitable for interaction with a small ligand. This is what this work is devoted to. Here we report the identification of a pocket located in close proximity to the RBD binding site with hACE2 and capable of interacting with more than a hundred substances that are approved by the FDA (Food and Drug Administration).

Methods

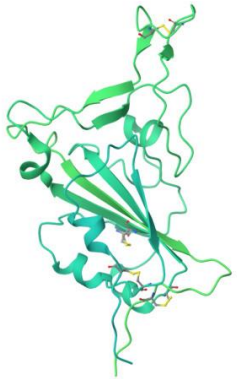
Software:

- Open Babel GUI (molecular weight filtration)
- MGLTools 1.5.7 (determining screening parameters)
- AutoDock Vina 1.1.2 (screening and assessment)
- Bash script (automation and uninterrupted operation)
- PyMol 1.8 (visualization)

Databases :

e-Drug3D (library of FDA approved drugs)

Protein Data Bank (RBD structure; ID: 7T9L)

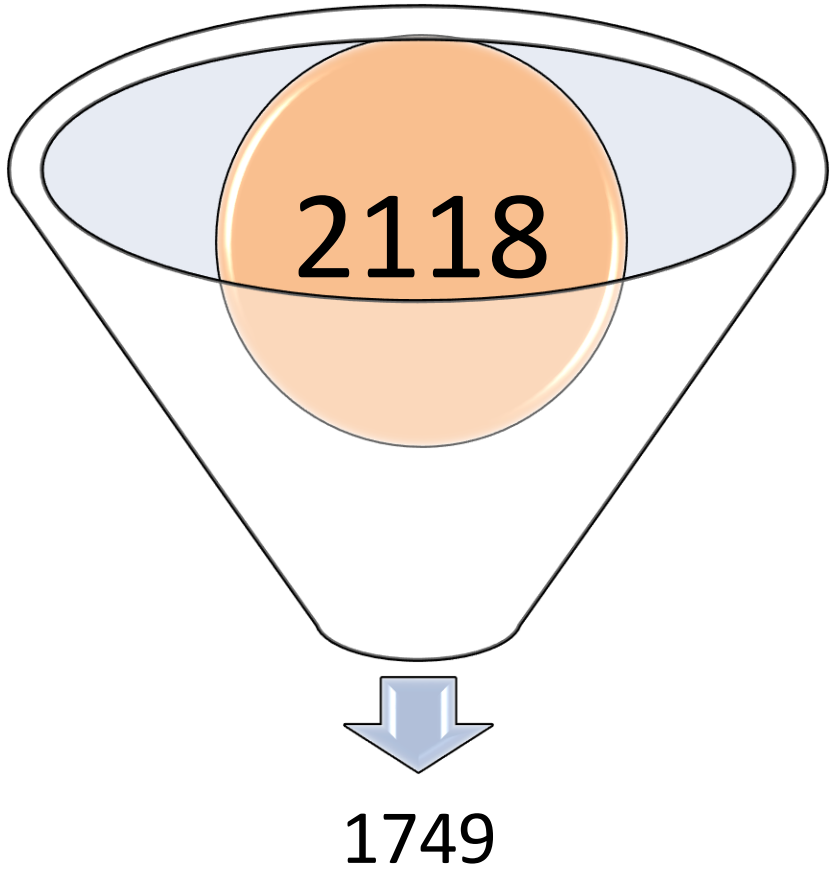


Results and discussion

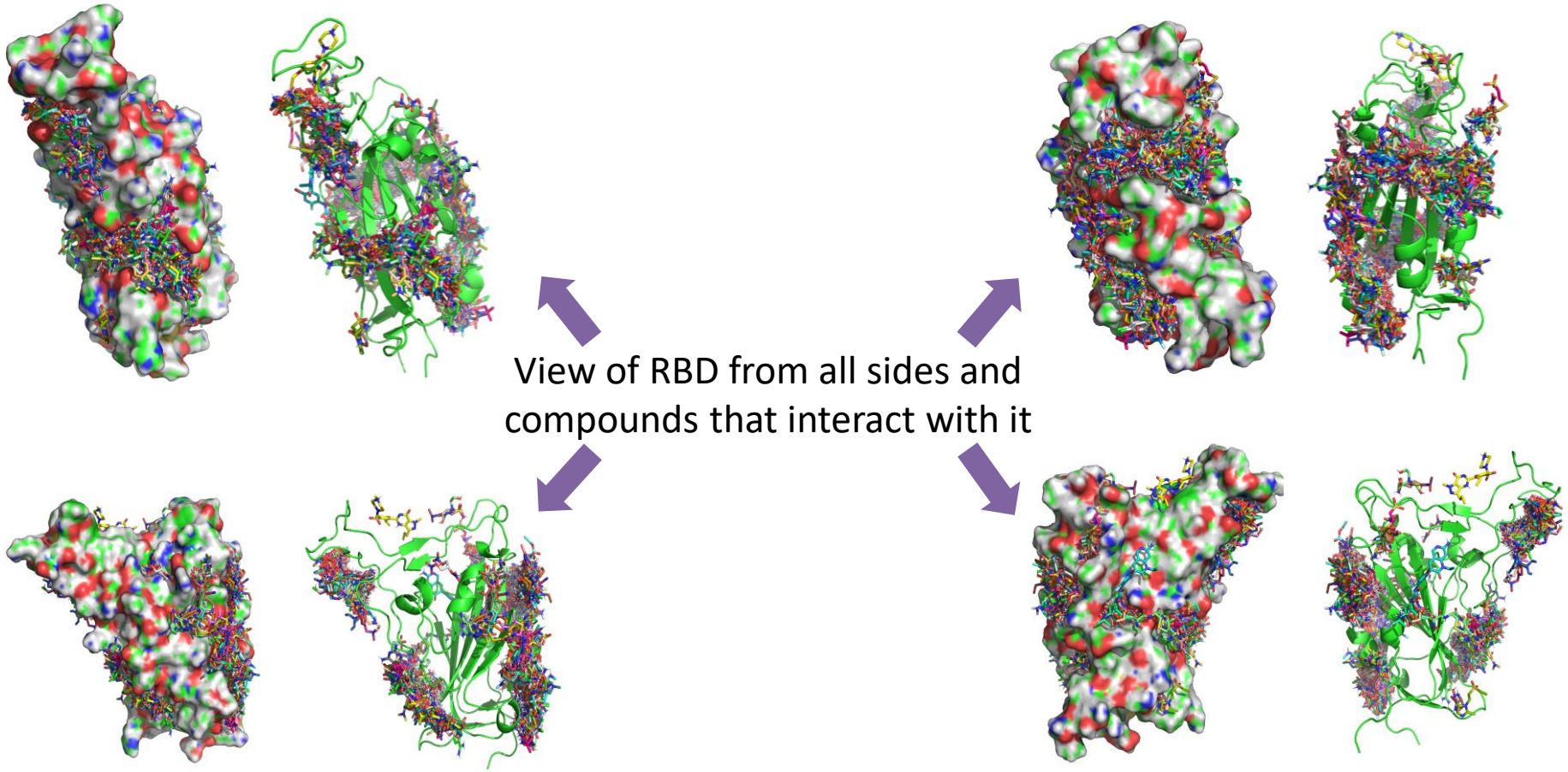
Molecular weight filtration

Filter: 100-500 Da (Lipinski's rule)

2118 ligands were filtered to 1749

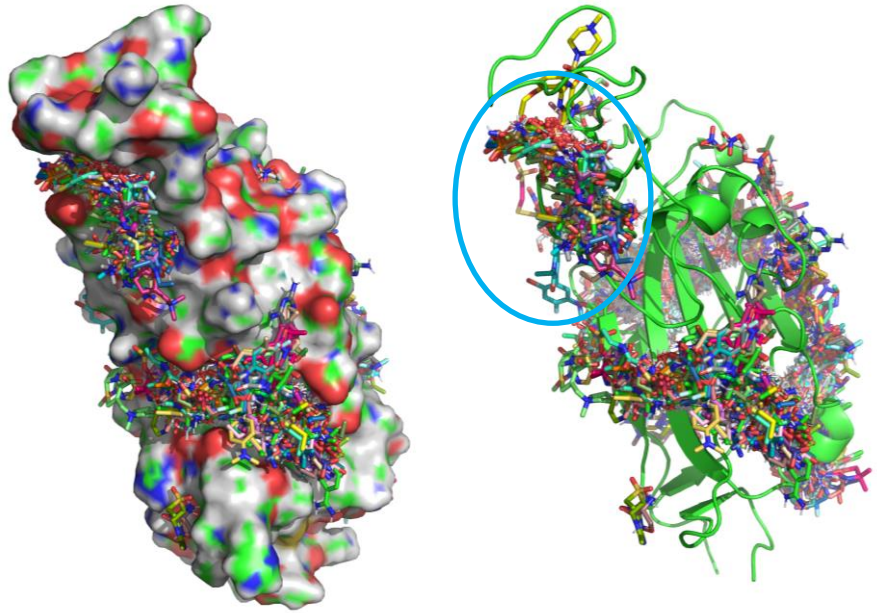


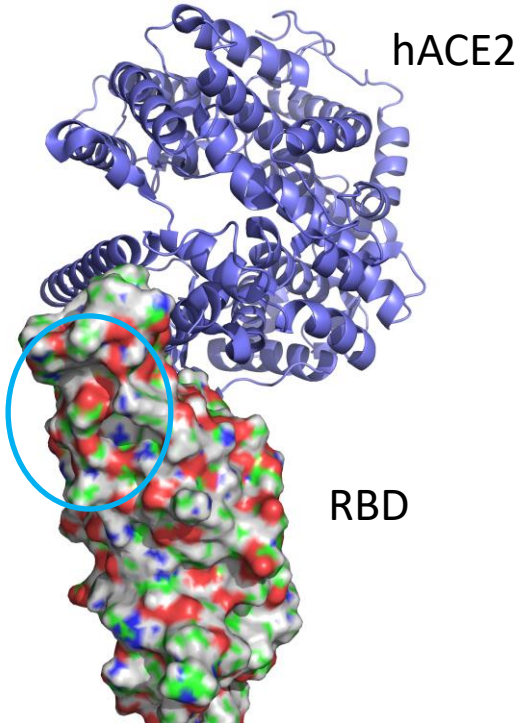
Docking and RBD surface map



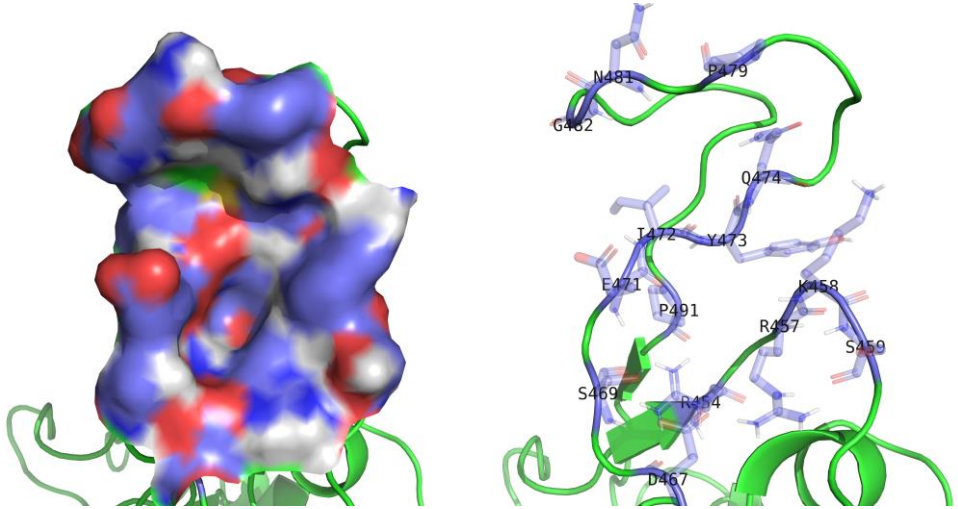
Pocket overview

One of the identified clusters of compounds (128 ligands) outlines a pocket in close proximity to the hACE2-binding site.

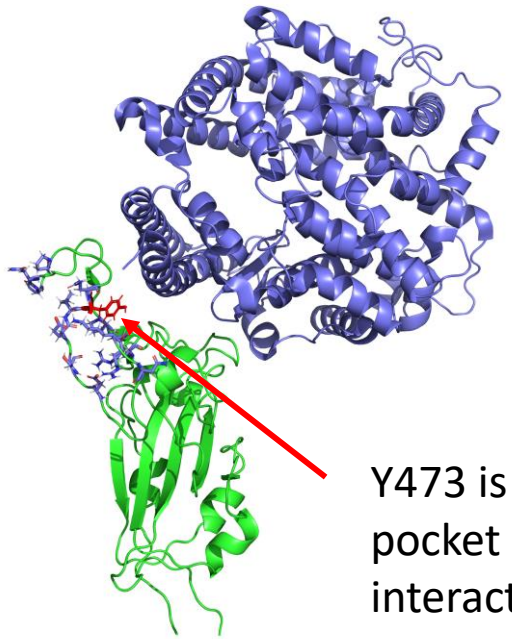




Pocket overview

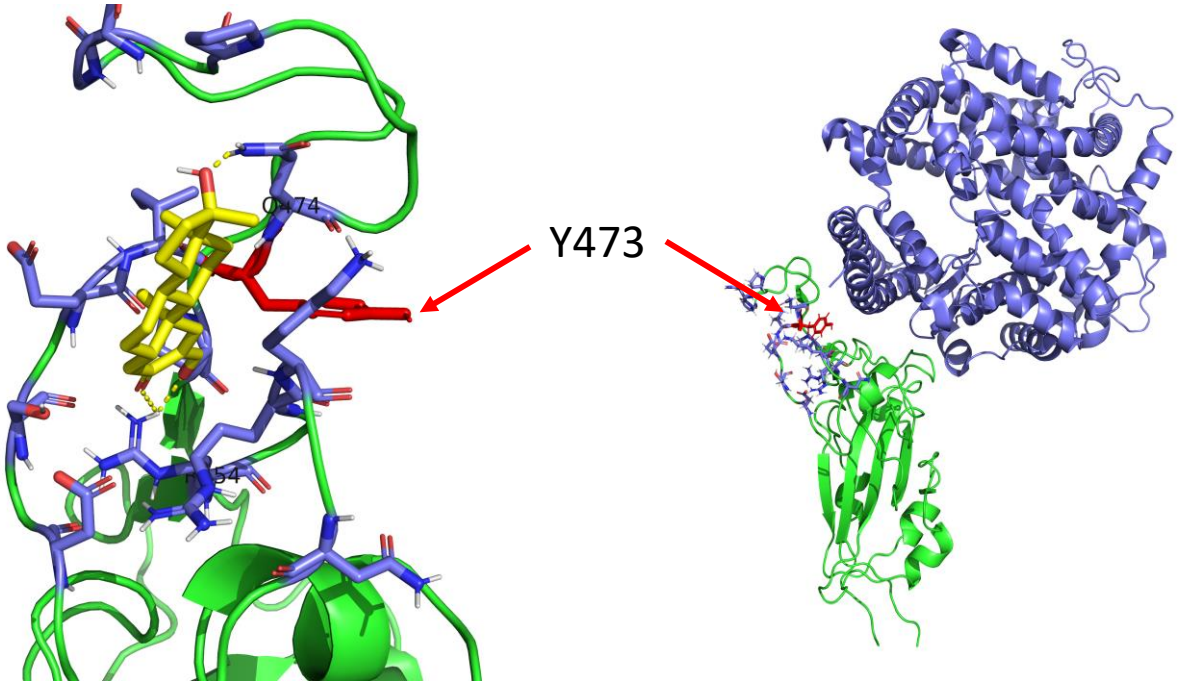


The pocket is formed by amino acids: R454, R457, K458, S459, D467, S469, E471, I472, Y473, Q474, P479, N481, G482 and P491



Y473 is both part of the discovered pocket and participates in the interaction with RBD and hACE2.

Oxymetholon in the pocket (example of interaction of a small molecule with RBD)



The affinity calculated by Vina score is -7.8 kcal/mol. Oxymetholon is positioned within the pocket via hydrogen bonds with R454 and Q474.

Conclusions

- In this work, the surface of the S-glycoprotein RBD of SARS-CoV-2 was investigated for the presence of promising pockets for further development and search for targeted antiviral compounds. The use of structures of FDA-approved drugs in the molecular weight range of 100-500Da for this blind docking allowed us to limit ourselves to only pockets suitable for binding drug-like molecules at the initial stage.
- Thus, a clearly defined pocket was identified in the immediate proximity of the RBD/hACE2 interaction site. It was able to interact with 128 ligands and consists of fourteen amino acids - R454, R457, K458, S459, D467, S469, E471, I472, Y473, Q474, P479, N481, G482 and P491. Oxymetholon had the best docking score of -7.8 kcal/mol among those ligands. It should be noted that one of the amino acids - Y473, which is part of the pocket, also directly contacts hACE2 during its interaction with the RBD.
- Therefore, the discovered pocket can be considered worthy of attention during the initial stages of development and search for anti-coronavirus drugs targeting the RBD of S-glycoprotein.

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Acknowledgments

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