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In silico identification of a potential inhibitor of the SARS-CoV-2 S-glycoprotein receptor-binding domain interaction with human ACE2

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pharmaceuticals MDPI

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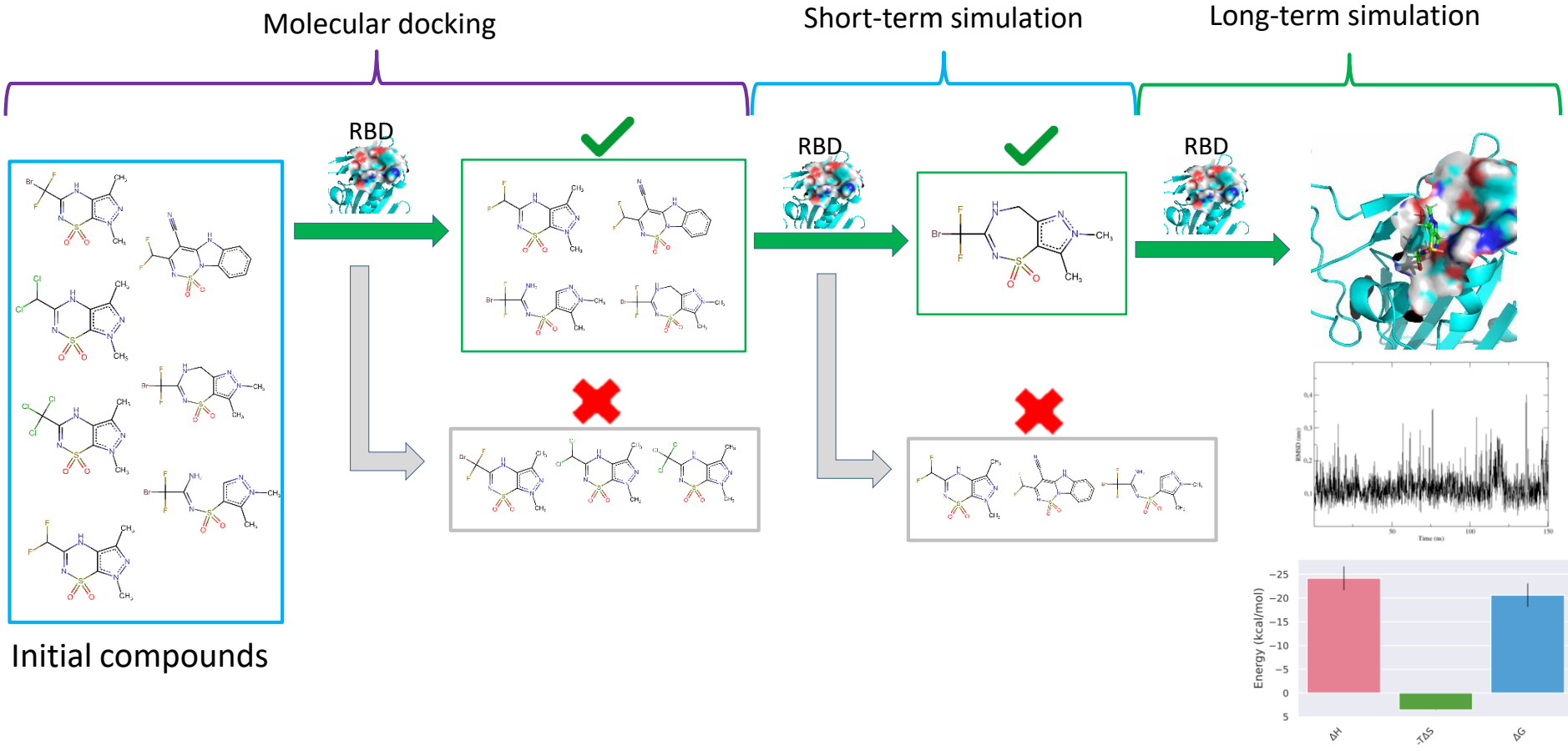
Graphical Abstract



Abstract:

Introduction: SARS-CoV-2 is an emerging pathogen that has strongly affected humanity over the past few years. Its S-glycoprotein receptor-binding domain provides the primary recognition of the host cell and initiates the viral penetration.

The goal of our work was to find potential inhibitors of the entry stage of the SARS-CoV-2 life cycle.

Methodology: firstly seven investigated compounds were prepared by generating their three-dimensional coordinates and protonating according to neutral pH in the OpenBabel ObGUI interface. Next, the mini-library was docked into the RBD interaction site with hACE2 using the AutoDock Vina. Part of the target amino acid residues was considered mobile. Based on the affinity assessment, four substances were selected for research in a simulation experiment implemented within the CHARMM-GUI, GROMACS and gmx_MMPBSA functionality.

Results: only four out of seven studied compounds were characterized by the optimal initial pattern of interactions and the calculated affinity. Further simulation studies allowed to discard three more on the basis of their dissociation from the docking site within 5ns from the simulation beginning. The last compound pyrazolothiadiazepine 1794 had an optimal position and the RMSD value of 1-2 Å during 150ns of simulation. At the same time, the calculated binding free energy of 1794 with RBD was -20.59 kcal/mol.

Conclusion: on the basis of molecular dynamics simulation analysis of the ligand-receptor complex, compound 1794 was selected as a potential inhibitor of the SARS-CoV-2 RBD interaction with human ACE2. It is characterized by the RMSD within 1-2 Å and a calculated ΔG of -20.59 kKal/mol.

Keywords: SARS-CoV-2, RBD, hACE2, drug, GROMACS, gmx_MMPBSA

Introduction

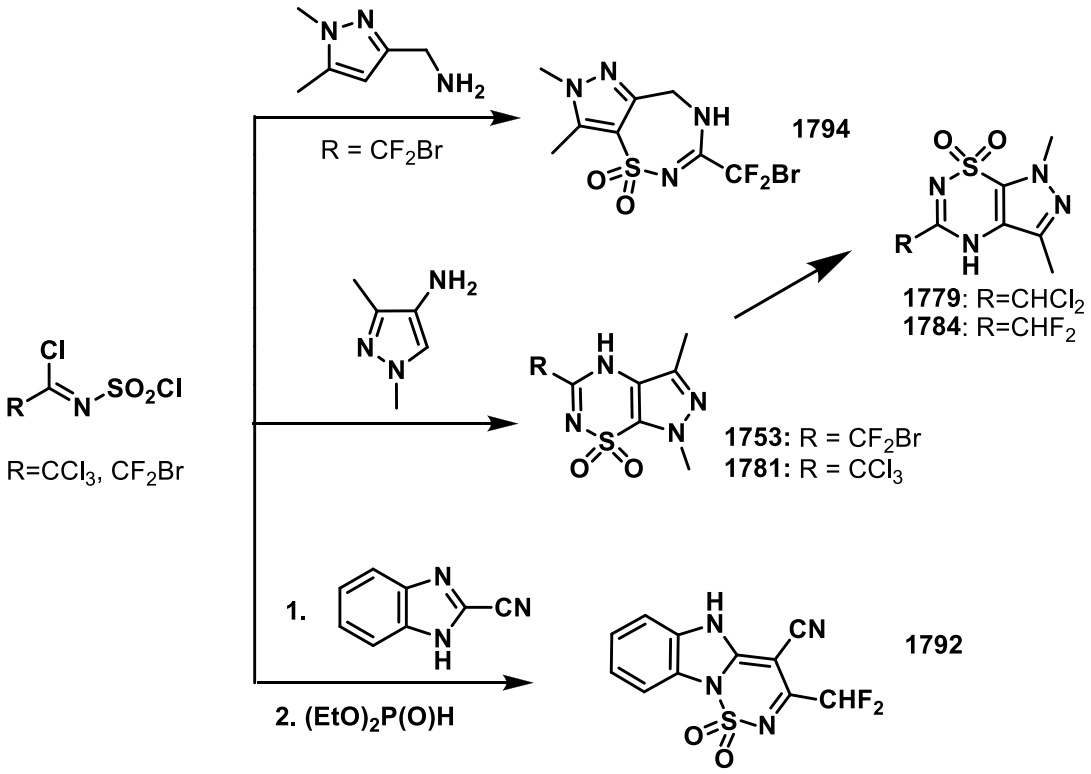
The new coronavirus, known as SARS-CoV-2, caused the most massive pandemic of the early 21st century, with at least 6.5 million reported deaths among more than 676 million cases. It was not until the spring of 2023 that the WHO reported the beginning of a reduction in the SARS-CoV-2 impact on the global health care system. However, this is a consequence of the massive increase of both post-vaccination and convalescent immunity among the population, and not of overcoming the pathogen as a whole. Moreover, effective and affordable drugs have not yet been developed.

The main factor that enabled the transspecies transfer of the new coronavirus is its S-glycoprotein and, in particular, the receptor-binding domain (RBD). This is confirmed by the fact that it is the S-glycoprotein that contains the largest number of changes compared to the genetically closest relative of SARS-CoV-2 – RaTG13. Along with the principle ability to infect human cells, this increases the affinity for ACE2 and the ability of this pathogen to enter the host cell.

The purpose of this work is virtual screening and simulation studies of seven newly synthesized compounds for their potential inhibitory activity on the interaction of the SARS-CoV-2 S-glycoprotein RBD with hACE2.

Results and discussion

Chemical synthesis

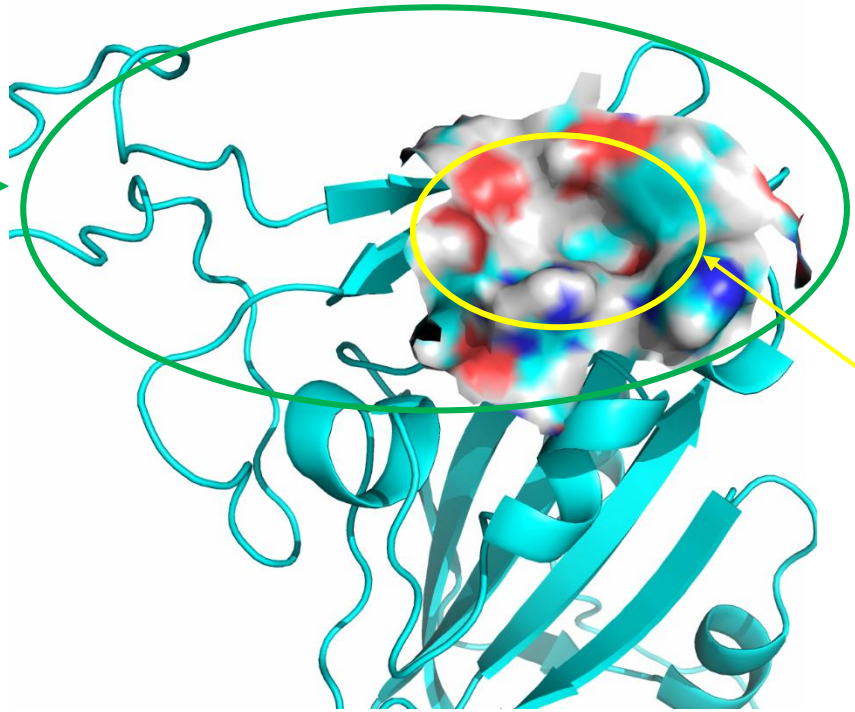


Results and discussion

Molecular dynamics simulation to determine topological features of RBD

CHARMM-GUI, GROMACS
- Glycoprotein
- 100ns
- Physiological conditions

Site of RBD interaction with hACE2



Promising for drug development RBD caveola

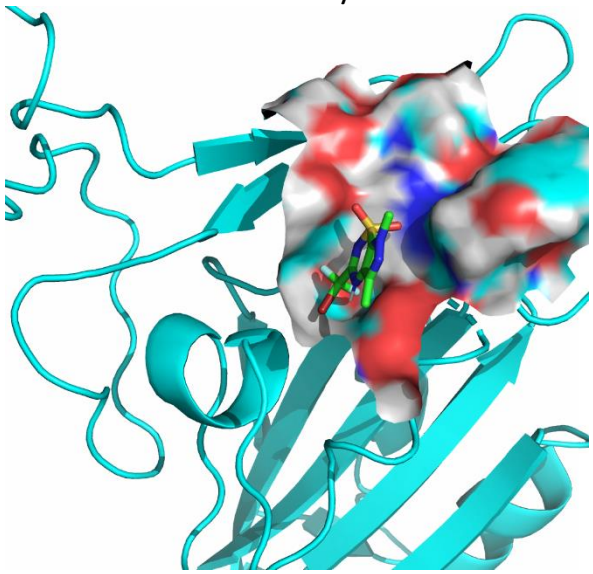
PDB ID: 7T9L

Results and discussion

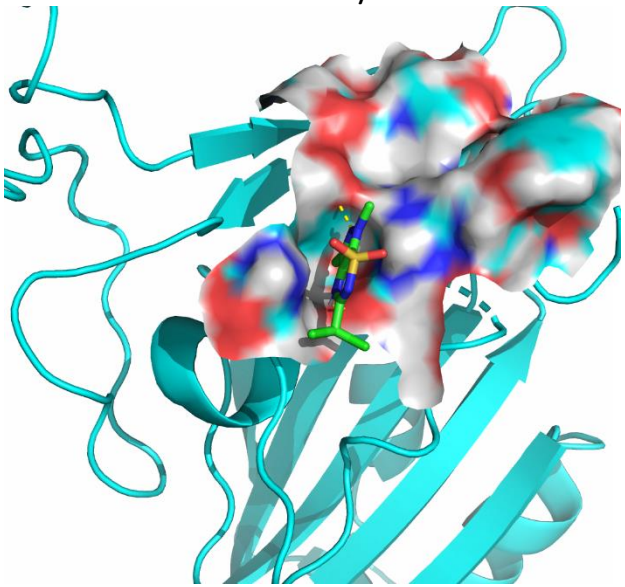
Molecular docking of the library of studied compounds

AutoDock Vina 1.2.3
- PDB ID: 7T9L
- Residues R403, E406, S496, Y501 and H505 were flexible
- Grid center: 45.485*57.936*57.448
- Grid size : 40*40*40
- Exhaustiveness: 32

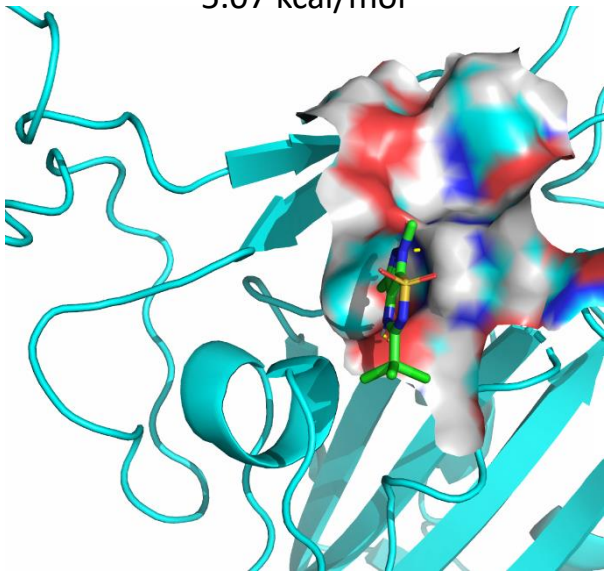
1753
-5.276 kcal/mol



1779
-5.625 kcal/mol



1781
-5.07 kcal/mol



Three substances had the highest level of affinity to the RBD outside the docking site and were rejected

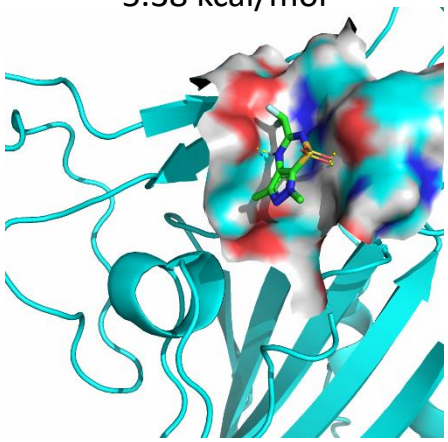
Results and discussion

Molecular docking of the library of studied compounds

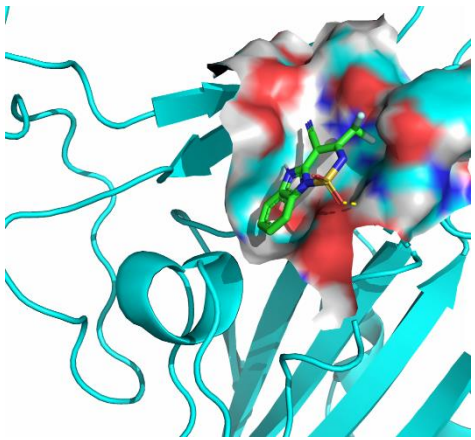
AutoDock Vina 1.2.3

- PDB ID: 7T9L
- Residues R403, E406, S496, Y501 and H505 were flexible
- Grid center: 45.485*57.936*57.448
- Grid size : 40*40*40
- Exhaustiveness: 32

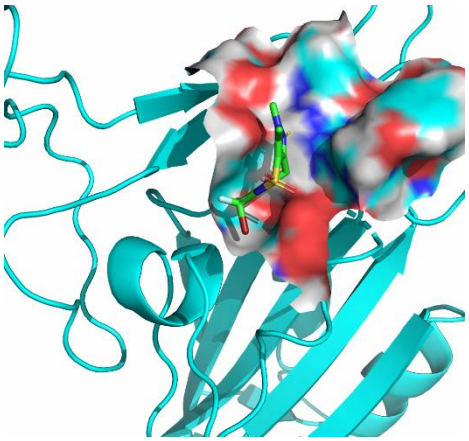
1784
-5.38 kcal/mol



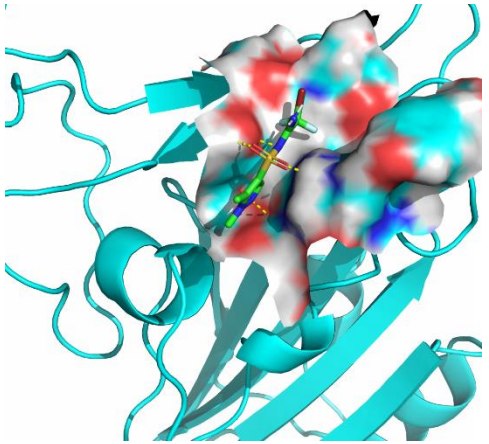
1792
-6.198 kcal/mol



1794
-5.413 kcal/mol



1797
-4.882 kcal/mol



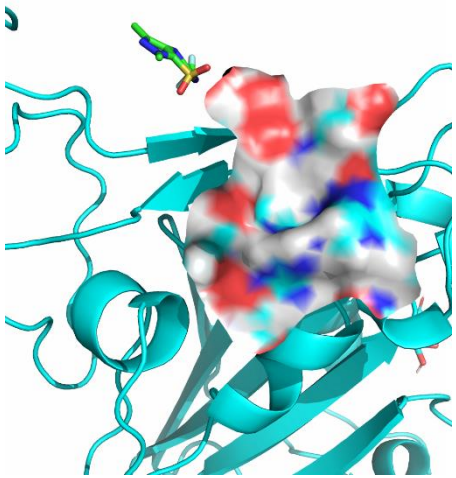
Four substances had the highest level of affinity to the RBD in the docking site and were selected for the next stage of the study

Results and discussion

Molecular dynamics simulation of selected compounds in complex with RBD (short-term simulation)

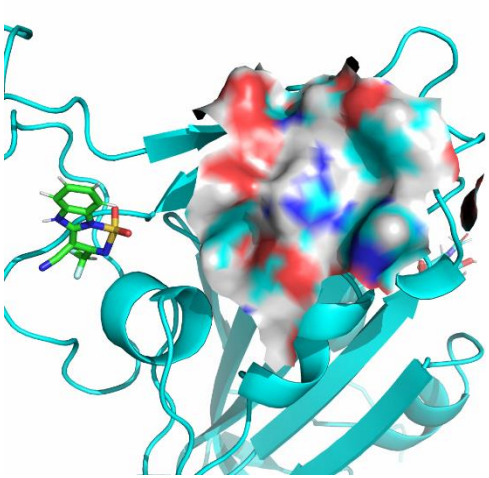
CHARMM-GUI, GROMACS
- Glycoprotein
- 25ns
- Physiological conditions

1784



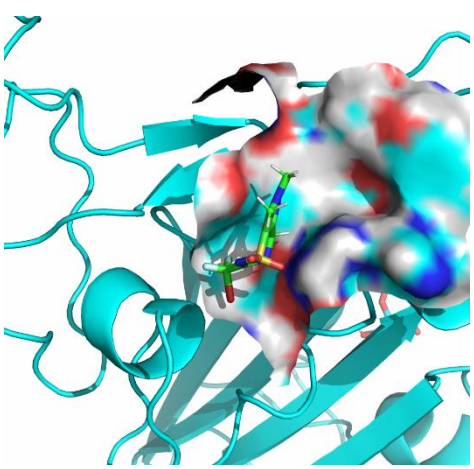
Leaves the docking site

1792



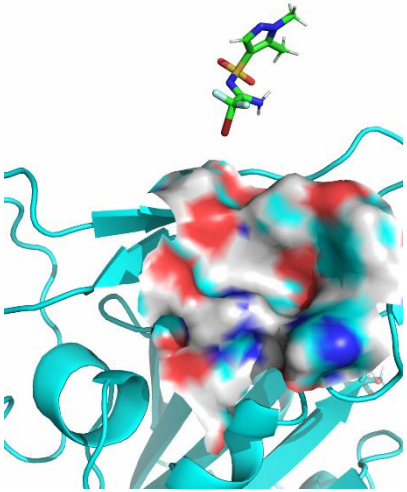
Leaves the docking site

1794



Stays in the docking site

1797



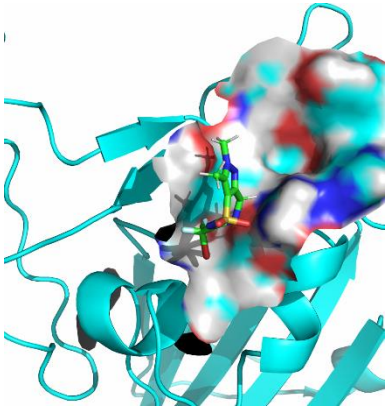
Leaves the docking site

Results and discussion

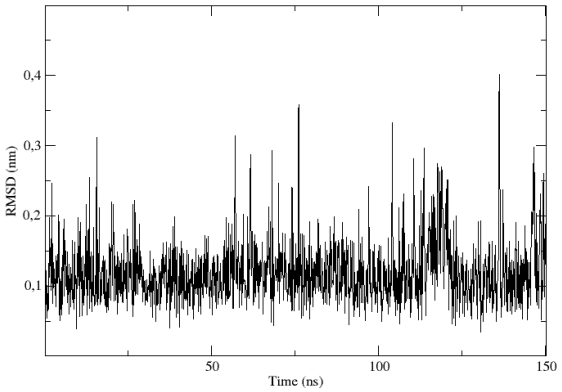
Molecular dynamics simulation of the compound **1794** in complex with RBD (long-term simulation)

CHARMM-GUI, GROMACS, gmx_MMPBSA
- Glycoprotein
- 150ns
- Physiological conditions
- MMPBSA

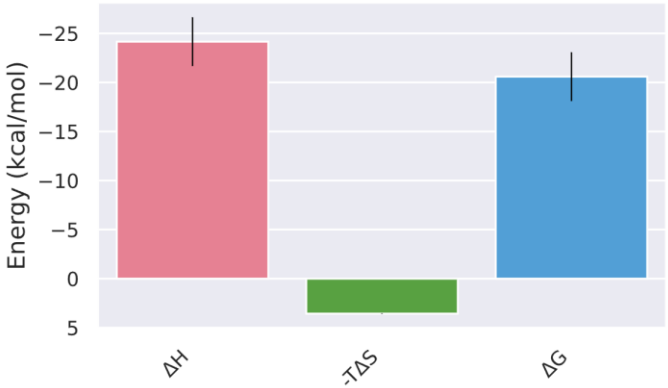
1794 doesn`t leave its docking site until the end of the simulation



1794 RMSD doesn`t exceed 2 Å



The binding free energy of 1794 with RBD is -20.59 kcal/mol



Compound 1794 forms a stable complex with the SARS-CoV-2 S-glycoprotein RBD

Conclusions

Within the scope of this work, seven newly synthesized low-molecular-weight compounds were investigated by in silico methods for their affinity to a predefined caveola within the site of interaction of the SARS-CoV-2 S-glycoprotein RBD with human ACE2. From the entire mini-library, substances 1753, 1759 and 1781 were rejected at the docking stage due to their highest affinity score obtained for sites outside the docking area. Instead, compounds 1784, 1792 and 1797 were rejected after a short-term molecular dynamics simulation in complex with the target. Within 5 ns from the beginning of the simulation, they all left the docking site. Only the pyrazolothiadiazepine 1794 was selected for the final long-term simulation study. This substance constantly kept its position within the interaction site of hACE2 and RBD. It was characterized by a close to optimal root-mean-square deviation within this complex and had a significant energy gain -20.59 kcal/mol calculated by the MMPBSA method.

Accordingly, we believe that compound 1794 has a significant potential to exhibit biological activity against the SARS-CoV-2, in particular, as an inhibitor of the S-glycoprotein receptor-binding domain interaction with human surface angiotensin-converting enzyme 2.