EUCHEMBIOJ

The European Chemistry and Biotechnology Journal
Eur. Chem. Biotechnol. J. 4: 14-23 (2025)

RESEARCH ARTICLE

Identification of new candidate molecules against SARS-CoV-2 through docking studies

Punar Aliyeva [1] | Beyza Yilmaz [2] | Doruk Alp Uzunarslan [3] | Vildan Enisoglu Atalay [4*]

[1] Uskudar University, Graduate School of Science, Department of Molecular Biology, 34662, Istanbul, Türkiye
ROR ID: 02dzjmc73

[2] Uskudar University, Graduate School of Science, Department of Biotechnology, 34662, Istanbul, Türkiye
ROR ID: 02dzjmc73

[3] Uskudar American Academy, 34674, Istanbul, Türkiye

[4] Informatics Institute, Computational Science and Engineering, Istanbul Technical University, 34469, Istanbul, Türkiye
ROR ID: 059636586

[*] **Corresponding author:** E-mail: enisogluatalayv@itu.edu.tr ; Ph.: +90 (212) 444 1 488; Fax: +09 (212) 285 29 10

Citation: Aliyeva, P., Yilmaz, B., Uzunarslan, D.A., & Enisoglu-Atalay, V. (2025) Identification of new candidate molecules against SARS-CoV-2 through docking studies. *The European chemistry and biotechnology journal*, 4, 14-23. https://doi.org/10.62063/ecb-40

Peer review: Double Blind Refereeing.

Received: 23.10.2024
Accepted: 16.05.2025
Online first: 27.05.2025

Abstract

The recent outbreak of a new coronavirus disease known as COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a highly contagious and pathogenic viral infection that has spread worldwide. Coronaviruses are known to cause disease in humans, other mammals, and birds. Although specific therapeutics and vaccines require efforts in this direction, reaching the world's population with mutations of the virus can be a difficult target. The major proteases of coronavirus play a critical role during the spread of the disease and therefore still represent an important target for drug discovery. As of now, there is still no official treatment for infected patients. In this study, bioinformatics-based molecular docking studies were performed to identify potent inhibitors of novel candidate molecules against the spike protein S of SARS-CoV-2. The affinities of ligand molecules thought to be effective in the treatment of SARS-CoV-2 disease were investigated. For this purpose, 1,615 different FDA-approved drug ligand molecules were retrieved from ZINC15 database. Crystallographic structure of spike protein S of SARS-CoV-2 was retrieved from Protein Data Bank (PDB). Initial virtual screening was performed using *qvina-w*, an accelerated version of AutoDock Vina optimized for rapid docking, to evaluate binding affinities of all 1,615 compounds against the spike protein. The top 10 ligands with the most favorable binding affinities were selected for further analysis. These ligands were docked to the target protein with Autodock Vina. The complexes were first solvated and then run through Molecular Dynamics (MD) simulations, utilizing NAMD. The binding energies were computed through these interactions, which are used to compare the affinities of the ligands to the target protein. Ultimately, 10 different ligands

capable of inhibiting the spike protein of SARS-CoV-2 were selected and compared based on their affinities.

Keywords: Coronavirus, in silico, Molecular Docking, Drug Development

Introduction

The acute respiratory infection that we know as the novel coronavirus SARS-CoV-2 was first identified in Wuhan China in the year 2019 (Petersen et al. 2020). This infection is highly contagious and can be transmitted via droplet and contact.Coronavirus (CoV) belongs to the family Coronaviridae, suborder Cornidovirineae, and order Nidovirales. According to the phylogenetic analysis, the Coronaviridae family can be classified into 4 genera, namely alpha, beta, delta, and gamma (Payne 2017). Human and animal cells are both susceptible to infection by the single stranded RNA virus known as the coronavirus, which has a positive virulence. Human coronaviruses are among the rapidly evolving viruses, because of their high recombination rate and nucleotide element dominance (Fehr and Perlman 2015). Several recent reports, both genome wide and at the receptor level provided unique insights on many characteristics of the SARS-CoV-2 virus. One of these characteristics include the ability of different variants of SARS-CoV-2 to bind to Angiotensin-Converting Enzyme 2 (ACE2) cell receptors (Letko et al 2020). It is the binding of the spike protein (S) to the ACE2 receptor that allows SARS-CoV-2 to enter cells, as it facilitates the initiation of viral replication (Shang, J et al, 2020; Wang et al 2020).

SARS-CoV-2 is a virus with a long, single-stranded RNA genome, about 30,000 bases in length. This genome is one of the largest among all known RNA viruses, which boosts the virulence of the virus through reduced dependence on host cells for replication. The virus itself is small, measuring between 50-200 nanometers, and is covered with spike-like proteins that help invade human cells. SARS-CoV-2 is responsible for causing Severe Acute Respiratory Syndrome (SARS), which affects the respiratory system and can lead to serious complications (Payne, 2017). The symptoms of infection can vary widely among individuals. While some patients experience mild, cold-like symptoms, others suffer from severe respiratory distress or long-term complications, often referred to as “long COVID.” This variability in how the virus impacts individuals highlights the complexity of SARS-CoV-2 and its interactions with the human body.

Coronaviruses display spherical structure and include the following four main types of structural proteins; membrane (M), envelope (E), nucleocapsid (N) and spike (S) protein (Fehr and Perlman, 2015). Membrane protein lies within the range of 25 to 30 kDa and has three transmembrane N-terminal domains, a glycosylated ectodomain and a C terminal domain (Armstrong et al., 1984). The M protein is diamiamic protein that fuses other outer structural proteins, foreboding the virus to bud out (Neuman et al., 2011). Envelope protein has an approximate mass of about 8 to 12 kDa (Schoeman and Fielding, 2019). The E protein consists of the N terminal ectodomain and C terminal endodomain (Nietto-Torres et al., 2014). The E protein increases the pathogenicity of the virus by acting on its ion channel as transmembrane proteins during the process of budding and the release of the virus (Li et al., 2014). The N protein has N terminal and C terminal domains.

The N protein is rich in phosphate esters and phosphates in general (Stohlman and Lai, 1979). Because of the strong binding of N proteins to viral RNA, the N protein associates with the viral RNA genome and encapsulates it (Kuo and Masters 2013). The N protein assists in the packaging of the

viral RNA genome into the replicase-transcriptase complex (RTC) and afterwards the virus genome into the viral virus (Hurst et al. 2013).

Spike protein has a vital role in SARS-CoV-2 virus transmission (Shang et al., 2020). Attachment initiates with the trimetric spike protein's S1 subunit's interaction with ACE2 receptors in the heart, kidneys, and lungs (Hamming et al., 2004). S1 and S2 separation in the SARS-CoV-2 spike protein takes place owing to the presence of the proprotein convertase (PPC) section (Walls et al., 2020). The S protein is subsequently cleaved at the host cell membrane by the transmembrane serine protease 2 (TMPRSS2) which results in the release of S1 subunit while triggering the S2 subunit to become rearranged to a post-fusion conformation that assists in the merging of the viral and host cell membranes (Bestle et al., 2020). The peptide domain that is able to modulate this action comes from the S2 subunit and is activated via receptor recognition, allowing it to breach the host cell membrane (Xiu et al., 2020). Delta and Omicron variants have highlighted the importance of targeting conserved viral elements, as these variants exhibit increased transmissibility and resistance to neutralizing antibodies (Shuai et al., 2022).

The primary objective of molecular docking is to characterize and predict molecular recognition, through structural (identifying alternate binding modes) and energy-wise compatibility. Computer-based methods shorten the drug design process, providing low cost and speed drug development environments, while, contributing to the analysis of the interaction between ligands and the target protein structure by calculating the binding affinity (Kitchen et al., 2004). *In silico* studies, molecular docking in particular, have accelerated the identification of potential inhibitors targeting SARS-CoV-2 proteins. Examples include the identification of drugs that could bind to the spike protein receptor-binding domain through docking studies (Garg et al., 2021; Santos-Martins et al., 2021). Computational techniques have been employed for fast, affordable, and efficient compound screening, paving the way for drug discovery.

In this study, molecular docking simulations are used to identify novel molecules capable of inhibiting the spike protein found in SARS-CoV-2. By evaluating binding affinities and physicochemical properties of ligand candidates, this work aims to contribute to the ongoing efforts of developing therapeutic strategies against SARS-CoV-2 and its evolving variants. FDA-approved molecules identified as inhibitors of the relevant target structure through the ZINC15 database were included in the study as ligand molecules.

Materials and methods

To obtain the crystal structures of the proteins important for SARS-CoV-2, the ACE2-linked structure with PDB ID 6M0J (Figure 1) at 2.45 Å resolution was selected from the Protein Data Bank (https://www.rcsb.org/) database (Lan et al., 2020). In order to perform multiple docking operations in a concise manner, it was essential to define a specific region of interest on the protein surface where ligand binding is most likely to occur. The gridbox center coordinates for 6M0J were determined as x=-31.454, y=29.553, z=21.871 and a gridbox box with a size of 40x40x40 $Å^3$ was determined. In this study, 1,615 different FDA-approved molecules were retrieved from the ZINC15 database (https://zinc15.docking.org). These molecules were then docked to the target protein. Through Autodock Vina, the binding affinities of the candidate molecules were scored and compared. The obtained physicochemical parameters of the ligand candidate moleculesfor effective treatment of SARS-CoV-2 disease were taken into consideration. All the docking studies were implemented using Autodock Vina (Eberhardt et al., 2021). After docking studies were performed, the interaction maps

of the ligands with the target protein structures were investigated in detail. The topmost 10 ligands were selected ranked by their binding affinities. These ligands were simulated for 2 nanoseconds using NAMD. Subsequently, the overall energy change was observed between the ligands and the target protein.

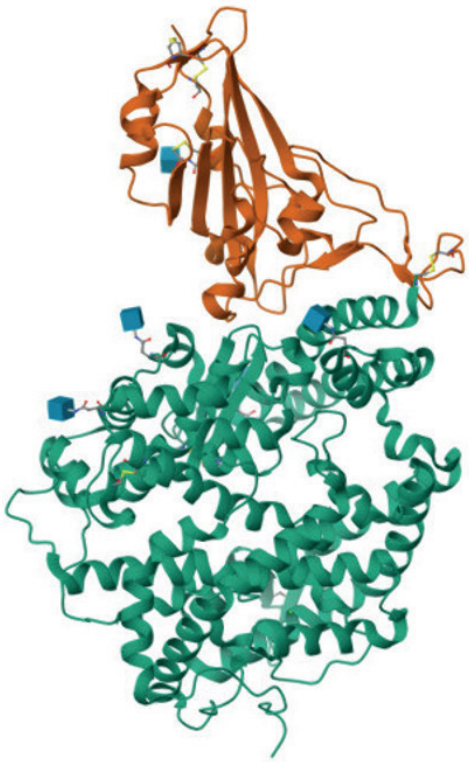

Figure 1. Crystal structure of SARS-CoV-2 spike receptor-binding domain bound with ACE2.

Results and discussion

Table 1 shows molecular weights and lipophilicities of candidate molecules that are were docked against S spike protein of SARS-CoV-2. These physicochemical parameters, including molecular weight (Mw) and lipophilicity (logP), play a crucial role in determining the pharmacokinetic behavior of the ligands, such as absorption, distribution, and membrane permeability.

Table 1. Calculated Properties of the Investigated Ligands (Top 100 Ranked by Binding As

ZINC ID	Mw	logP	BE	ZINC000253387843	924.091	0.712	-8.7
ZINC000052955754	581.673	1.991	-10.1	**ZINC000252286876**	926.107	0.778	-8.7
ZINC000252286878	926.107	0.778	-9.7	**ZINC000253630390**	875.106	5.601	-8.6
ZINC000203757351	765.893	3.637	-9.2	**ZINC000150338819**	889.017	8.607	-8.4
ZINC000242548690	780.949	2.218	-9.1	**ZINC000068202099**	485.506	5.822	-8.2
ZINC000003927200	366.501	4.306	-8.8	**ZINC000001530886**	514.629	7.264	-8.2
ZINC000003978005	583.689	2.081	-8.8	**ZINC000100378061**	570.646	3.48	-8.2
ZINC000027990463	693.732	8.382	-8.8	**ZINC000000968264**	287.406	4.698	-8.2

ZINC000003784182	412.529	6.681	-8.2
ZINC000252286877	926.107	0.778	-8.2
ZINC000040430143	434.471	2.347	-8.1
ZINC000169621215	847.019	4.616	-8.1
ZINC000150588351	882.035	8.116	-8
ZINC000100013130	570.649	5.907	-8
ZINC000000538658	448.95	5.683	-8
ZINC000003985982	414.498	3.125	-8
ZINC000095617678	810.466	5.719	-8
ZINC000169289767	872.894	6.67	-8
ZINC000169621228	877.045	5.648	-8
ZINC000003932831	528.537	6.576	-8
ZINC000028232746	723.65	2.462	-7.9
ZINC000203686879	883.019	7.732	-7.9
ZINC000004175630	461.556	6.269	-7.9
ZINC000164528615	838.878	3.857	-7.9
ZINC000003918087	543.525	0.001	-7.8
ZINC000204073689	492.591	5.63	-7.8
ZINC000011681563	578.601	6.787	-7.8
ZINC000036701290	532.57	4.456	-7.8
ZINC000003927822	492.689	4.256	-7.8
ZINC000006716957	529.526	6.356	-7.8
ZINC000169621200	785.891	6.158	-7.8
ZINC000253632968	749.956	5.254	-7.8
ZINC000003872566	501.667	5.511	-7.7
ZINC000012503187	498.586	6.507	-7.7
ZINC000019632618	493.615	4.59	-7.7
ZINC000003831128	429.604	5.407	-7.7
ZINC000000538550	412.946	3.809	-7.7
ZINC000164760756	749.956	5.254	-7.7
ZINC000053683151	654.606	3.193	-7.7
ZINC000150338755	868.457	8.66	-7.7
ZINC000252286875	926.107	0.778	-7.7
ZINC000169621219	729.908	3.438	-7.7
ZINC000004213474	454.966	3.889	-7.6
ZINC000118912450	332.484	4.401	-7.6
ZINC000011616852	723.65	2.462	-7.6
ZINC000004213946	405.441	2.364	-7.6
ZINC000004214700	426.492	3.081	-7.6
ZINC000064033452	452.413	4.747	-7.6
ZINC000008220909	665.733	0.12	-7.6
ZINC000014261579	540.697	4.704	-7.6
ZINC000169289388	914.187	6.181	-7.6
ZINC000003917708	527.526	1.029	-7.6
ZINC000072318121	506.605	4.937	-7.6
ZINC000150338708	761.85	3.413	-7.6
ZINC000001612996	586.689	4.091	-7.5
ZINC000034089131	433.592	4.972	-7.5
ZINC000169621220	665.733	0.12	-7.5
ZINC000003882036	394.439	0.62	-7.5
ZINC000084758235	546.937	4.51	-7.5
ZINC000003860453	332.311	3.666	-7.5
ZINC000100073786	562.706	4.24	-7.5
ZINC000004074875	610.671	6.319	-7.5
ZINC000000897240	381.907	4.298	-7.5
ZINC000035902489	450.345	5.038	-7.5
ZINC000035328014	440.507	4.217	-7.5
ZINC000003816514	500.483	5.73	-7.5
ZINC000003920266	497.5	1.02	-7.5
ZINC000016052277	444.44	0.702	-7.5
ZINC000100017856	366.844	5.505	-7.5
ZINC000261527196	690.86	2.269	-7.5
ZINC000003993846	506.709	4.051	-7.5
ZINC000100370145	562.706	4.24	-7.5
ZINC000100013500	517.776	5.251	-7.4
ZINC000000643143	531.44	4.206	-7.4
ZINC000003931840	517.776	5.251	-7.4
ZINC000066166864	482.628	4.773	-7.4
ZINC000011617039	437.529	3.139	-7.4
ZINC000095551509	766.918	4.142	-7.4
ZINC000103105084	324.38	2.519	-7.4
ZINC000013831130	444.423	1.486	-7.4
ZINC000085537026	748.996	1.901	-7.4
ZINC000111460375	562.706	4.24	-7.4
ZINC000005844792	405.441	2.364	-7.4
ZINC000000004724	252.273	2.642	-7.4
ZINC000001539579	348.486	6.104	-7.4
ZINC000218037687	868.948	4.957	-7.4
ZINC000169621231	958.24	6.197	-7.4
ZINC000043207238	444.524	2.968	-7.4
ZINC000030691420	408.922	2.021	-7.4
ZINC000053683271	690.86	2.269	-7.4
ZINC000150601177	894.127	7.687	-7.4
ZINC000306122005	540.708	1.43	-7.4
ZINC000009574770	812.018	4.929	-7.3

As demonstrated in Table 1, it is evident that the binding affinities of the candidate ligands to the S spike protein of SARS-CoV-2 vary significantly. -7.0 kcal/mol is acknowledged as a threshold for high protein-ligand binding affinity. As clearly shown on Table 1, multiple candidate ligands surpass this threshold with a relatively high margin. This underlines the fact that alternative options for highly affinitive ligands exist ubiquitously among FDA approved ligands.

Moreover, the 10 most suitable ligands compared based on Binding Affinities (kcal/mol) are put into molecular dynamics simulation for further analysis. The protein–ligand complex was subjected to a 2 nanosecond molecular dynamics simulation using Nanoscale Molecular Dynamics (NAMD) (Philips *et al.*, 2020). After the simulation was complete, visualization and trajectory analyses were performed using Visual Molecular Dynamics (VMD) (Humphrey, 1996). The system was solvated in a TIP3P water box, neutralized with counterions, and simulated under periodic boundary conditions using the CHARMM36 force field. Insights from these simulations will help identify ligands with both strong and stable interactions, potentially guiding future *in vitro* validation and drug repurposing efforts against SARS-CoV-2.

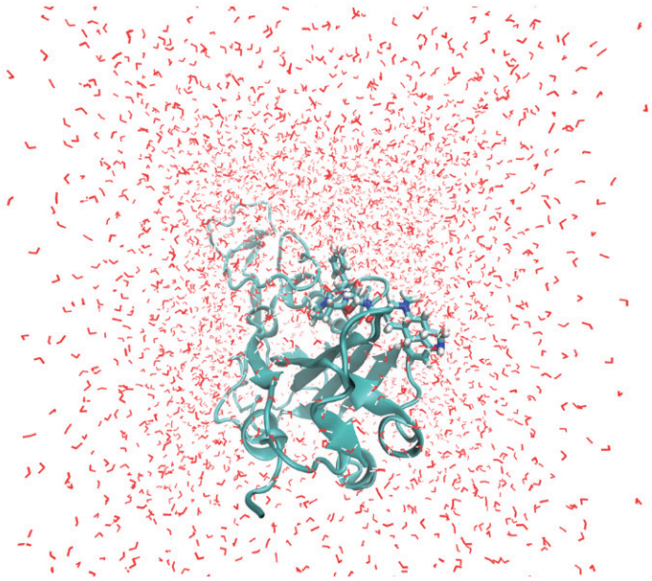

Figure 2. ZINC000052955754 Docked to spike protein S of SARS-CoV-2.

Figure 2 shows the complex formed by ZINC000052955754 and spike protein S of SARS-CoV-2. Taking Table 1 into consideration, this ligand shows high binding affinity towards the spike protein of SARS-CoV-2. After this initial docking analysis, the complex was subjected to molecular dynamics simulation to evaluate the stability and behavior of the ligand within the binding pocket over time. Non-bonded interactions between the ligand and the protein were calculated through NAMD to provide a better viewpoint on the inhibition feature of the ligand. Calculated frame-by-frame, the mean of interaction energy was calculated as **-62.811** kcal/mol. The negative value of the interaction energy suggests that the binding process is thermodynamically favorable and likely spontaneous under physiological conditions. This energy profile reinforces the notion that ZINC000052955754 forms a stable and energetically favorable complex with the spike protein.

Conclusions

This study identified potential candidate molecules for inhibiting the SARS-CoV-2 spike protein by molecular docking studies. Among the 1,615 compounds screened, the top ten candidates were further investigated through molecular docking and molecular dynamics simulations. The frequent and significant interactions between these ligands and the amino acids suggest their potential as inhibitors against SARS-CoV-2 spike protein. Furthermore, ligand with the ZINC ID of ZINC000052955754 demonstrated a strong and spontaneous interaction with the spike protein, supported by a mean interaction energy of -62.811 kcal/mol. These findings emphasize the potential of repurposing existing drugs as effective inhibitors of SARS-CoV-2. *In silico* methodologies applied in this study provide a cost-effective and efficient pathway for drug discovery. These results align with the understanding that structural compatibility between the ligand and active site is crucial for achieving high binding affinity. Moreover, the results reinforce the importance of structural complementarity and physicochemical optimization in achieving high-affinity protein–ligand interactions. Future work should focus on experimental validation through *in vitro* and *in vivo* assays to confirm the therapeutic potential of these candidates. Expanding the compound library and enhancing computational accuracy will further strengthen the applicability of such approaches in addressing current and emerging viral threats.

Acknowledgements

None.

Funding

None.

Conflict of interest

The authors declare no conflict of interest.

Data availability statement

Data can be obtained from the corresponding author upon a reasonable request.

Ethics committee approval

Ethics committee approval is not required for this study.

Authors' contribution statement

The authors acknowledge their contributions to this paper as follows: **Study conception and design**: P.A., B.Y., D.A.U., V.E.A.; **Data collection**: P.A., B.Y., D.A.U., V.E.A.; **Analysis and interpretation of results**: P.A., B.Y., D.A.U., V.E.A.; **Manuscript draft preparation**: P.A., B.Y., D.A.U., V.E.A. All authors reviewed the results and approved the final version of the manuscript.

ORCIDs and emails of the authors

Punar Aliyeva | ORCID 0000-0002-2868-0736 | pnar_aliyeva@mail.ru

Beyza Yilmaz | ORCID 0009-0007-5768-5070 | beyza.yilmaz@st.uskudar.edu.tr

Doruk Alp Uzunarslan | ORCID 0009-0001-4223-7984 | duzunarslan27@my.uaa.k12.tr

Vildan Enisoglu Atalay | ORCID 0000-0002-9830-9158 | enisogluatalayv@itu.edu.tr

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