



Molecular Docking and Dynamics Simulation of a Screening Library from Life Chemicals Database for Potential Protein-Protein Interactions (PPIs) Inhibitors against SARS-CoV-2 Spike Protein

**Hasanain Abdulhameed Odhar^{1*}, Salam Waheed Ahjel¹, Ahmed Fadhil Hashim¹
and Ali Mahmood Rayshan¹**

¹*Department of Pharmacy, Al-Zahrawi University College, Karbala, Iraq.*

Authors' contributions

This work was carried out in collaboration among all authors. Author HAO conceived project idea, performed computational work and wrote first draft of manuscript. Author SWA helped in interpretation of results and supervised project. Authors AFH and AMR carried out literatures search. All the authors read and approved final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i20A31350

Editor(s):

- (1) Dr. Arun Singh, Rohilkhand Medical College and Hospital, India.
- (2) Dr. Barkat Ali Khan, Gomal University, Pakistan.
- (3) Dr. Alyautdin Renad N, Scientific Centre for Expert Evaluation of Medicinal Products, Russia.

Reviewers:

- (1) Rafael Aparecido Carvalho Souza, Federal University of Uberlândia, Brazil.
 - (2) Muniza Shaikh, Dr. Panjwani Center For Molecular Medicine and Drug Research, ICCBS, University of Karachi, Pakistan.
 - (3) Rene Francisco Boschi Gonçalves, Aeronautics Institute of Technology, Brazil.
 - (4) Eduardo de Faria Franca, Federal University of Uberlândia, Brazil.
 - (5) Mohamad Zulkeflee bin Sabri, Universiti Kuala Lumpur (MICET), Malaysia.
- Complete Peer review History: <http://www.sdiarticle4.com/review-history/66801>

Original Research Article

Received 25 January 2021

Accepted 30 March 2021

Published 05 April 2021

ABSTRACT

The ongoing pandemic of coronavirus 2 represents a major challenge for global public health authorities. Coronavirus disease 2019 can be fatal especially in elderly people and those with comorbidities. Currently, several vaccines against coronavirus 2 are under application in multiple countries with emergency use authorization. In the same time, many vaccine candidates are under development and assessment. It is worth noting that the design of some of these vaccines depends on the expression of receptor binding domain for viral spike protein to induce host immunity. As such, blocking the spike protein interface with antibodies, peptides or small molecular compounds

*Corresponding author: E-mail: hodhar3@gmail.com;

can impede the ability of coronavirus 2 to invade host cells by intervention with interactions between viral spike protein and cellular angiotensin converting enzyme 2. In this virtual screening study, we have used predictive web servers, molecular docking and dynamics simulation to evaluate the ability of 3000 compounds to interact with interface residues of spike protein receptor binding domain. This library of chemicals was focused by Life Chemicals as potential protein-protein interactions inhibitor. Here, we report that hit compound 7, with IUPAC name of 3-cyclohexyl-N-(4-((1R,9R)-6-oxo-7,11-diazatricyclo [7.3.1.0^{2,7}] trideca-2,4-dien-11-yl) sulfonyl) phenyl) propanamide, may have the capacity to interact with interface of receptor binding domain for viral spike protein and thereby reduce cellular entry of the virus. However, in vitro and in vivo assessments may be required to validate these virtual findings.

Keywords: SARS-CoV-2; COVID-19; protein-protein interactions inhibitor; rule of four; docking; molecular dynamics simulation.

1. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative pathogen responsible for the ongoing pandemic of coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-2 is a novel RNA virus and has about 79% of genomic sequence identity with SARS-CoV, a previously identified beta-coronavirus [2]. SARS-CoV-2 can be transmitted mainly through exposure to respiratory droplets generated by infected persons. Airborne transmission by aerosols is also possible during aerosol generating medical procedures like intubation [3]. Upon exposure to SARS-CoV-2, the mean incubation period can range between 5.6 and 6.7 days after which symptoms of COVID-19 may develop [4]. Common clinical features of COVID-19 include fever, dry cough, shortness of breath, fatigue, myalgia, nausea, vomiting and diarrhea. The COVID-19 infection fatality rate (IFR) is estimated to be 0.68% in general with 95% confidence interval between 0.53% and 0.82%. COVID-19 fatality is usually the result of complications like pneumonia, acute respiratory distress syndrome (ARDS), cardiac injury, liver injury, kidney injury and coagulopathy [5,6]. Therapeutic options currently available to control COVID-19 complications involve oxygen supply, management of sepsis, use of corticosteroids, heparin and antiviral agents like Remdesivir [5,7–9]. According to World health organization (WHO), as of 18 February 2021, seven anti-COVID-19 vaccines are under emergency use authorization in multiple countries and more than 60 vaccine candidates are under clinical development [10]. Different platforms have been utilized to produce these COVID-19 vaccines like inactivated virus, protein subunit, recombinant viral-vector and nucleic acid (DNA and mRNA). Some of these vaccines have focused on the expression of full-

length SARS-CoV-2 spike protein inside human body to elicit immune response, other vaccines used only the receptor binding domain (RBD) of spike protein to induce immunity [11]. SARS-CoV-2 can infect susceptible host through interaction with angiotensin converting enzyme 2 (ACE2) on the surface of target cells. The receptor binding domain (RBD) of SARS-CoV-2 is located within S1 subunit of the viral spike protein [12]. Virtual alanine scanning approach have been used to determine the interacting residues at the interface of SARS-CoV-2 receptor binding domain and angiotensin converting enzyme 2. Identification of these interface residues is considered important to construct a protein-protein interactions (PPIs) inhibitor capable of blocking cellular entry of SARS-CoV-2 [13]. A three-dimensional illustration for the complex between RBD of SARS-CoV-2 spike protein and ACE2 can be seen in Fig. 1 (A). A close view for interaction interface of crystal complex can be seen in Fig. 1 (B). The sequence of amino acids for RBD of SARS-CoV-2 spike glycoprotein is presented in Fig. 1 (C), RBD residues involved in interaction with ACE2 are surrounded by orange line. In this virtual screening study, we have used a protein-protein interactions (PPIs) focused library of compounds from Life Chemicals database. Our aim was to identify potential inhibitor of SARS-CoV-2 spike protein binding to ACE2 thereby blocking viral entry to target cells. The chemical compounds in this library were curated based on rule of four (RO4) principle. According to rule of four, a compound may have the potential to inhibit protein-protein interactions (PPIs) if it possesses the following four chemical criteria: a molecular weight (M.W.) ≥ 400 g/mol, a calculated logarithm of partition coefficient (cLog P) ≥ 4 , the number of rings ≥ 4 and the number of hydrogen bond acceptor (HBA) ≥ 4 [14,15].

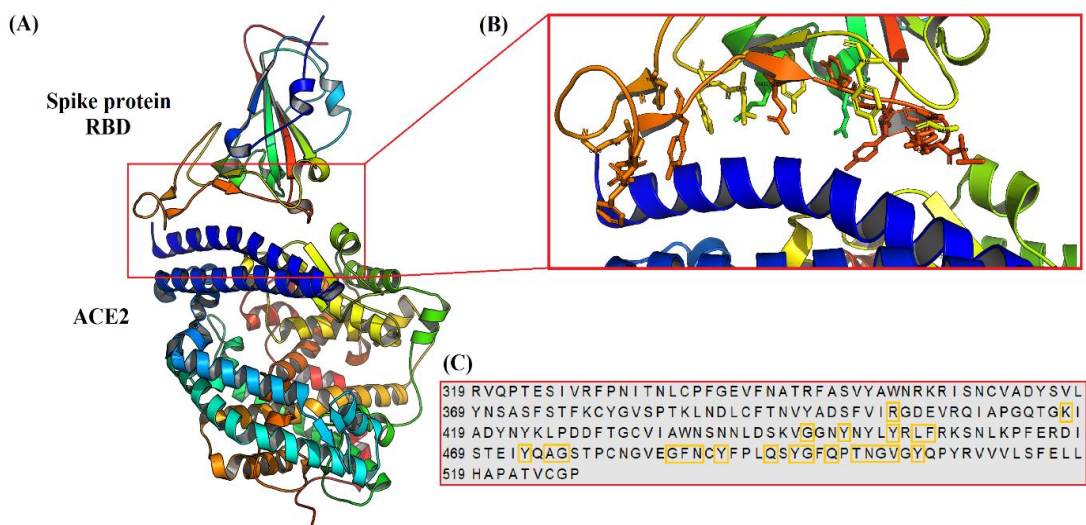


Fig. 1. (A) A three-dimensional view for 6LZG crystal complex between receptor binding domain RBD of SARS-CoV-2 spike protein and its receptor angiotensin converting enzyme 2 ACE2. (B) A close view for interaction interface between SARS-CoV-2 spike protein RBD and ACE2, the amino acid residues of spike protein RBD are shown as sticks. (C) The amino acids sequence of SARS-CoV-2 spike protein RBD is presented in one letter format, RBD residues that are involved in interaction with ACE2 are encircled by orange line

2. MATERIALS AND METHODS

2.1 Preparation of Receptor Binding Domain Crystal and Chemicals Database

The crystal complex of receptor binding domain RBD of SARS-CoV-2 spike protein and angiotensin converting enzyme 2 ACE2 was downloaded from protein data bank website, the identification code for the downloaded crystal PDB is 6LZG [16,17]. We have used UCSF chimera version 1.15 to prepare the crystal file for docking study and dynamics simulation [18]. By using UCSF chimera software, we have removed ACE2 peptidase domain (chain A) from 6LZG crystal, we have also removed any bound ligands, water molecules and ions. The residues sequence of chain B (receptor binding domain) was visualized as one letter format by using UCSF chimera. We have used 3000 compounds downloaded from Life Chemicals website as a screening library, this library of chemicals was focused by Life Chemicals as potential inhibitors for protein-protein interactions (PPIs) by using rule of four (RO4) filtration criteria. Based on RO4 principle, any compound may have the capacity to interfere with interactions between two proteins if it has the following criteria: a molecular weight ≥ 400 g/mol, a logarithm of

partition coefficient ≥ 4 , the number of hydrogen bond acceptor ≥ 4 and the number of rings ≥ 4 . Additionally, the compounds in this focused library have been enriched for sp³ hybridization of carbon atoms to ensure high level of three-dimensional diversity and hence sufficient drug-likeness score [14,15].

2.2 Structure-based Virtual Screening

We have used MCULE online drug discovery website to screen the downloaded chemicals library against the prepared crystal of SARS-CoV-2 spike protein RBD (chain B of 6LZG crystal) [19]. Here, we used a virtual screening workflow steps similar to those applied in our previously published researches [20,21]. In summary, we have used the default screening steps with the addition of REOS (Rapid Elimination of Swill) filter to reduce possibility of frequent and non-selective hits. The MCULE website employs AutoDock Vina tool to perform structure based virtual screening [22]. Also, this online drug discovery platform uses AutoDock tools to add polar hydrogen atoms and Gasteiger charges to the uploaded crystal [23]. We have used a binding site area of (X: 30, Y:30, Z:30) Angstrom while the coordinates were (X: -33, Y: 26, Z: 7.5). The final hits were ranked according to their least binding energy to the receptor binding domain (RBD) of SARS-CoV-2 spike

protein crystal (chain B). According to the minimum binding energy rank, we have selected the top ten hits for further virtual characterization and visualization. For each compound of these top ten hits, we have saved the complex of ligand and protein with least binding energy pose as PDB file. The generated PDB file was then visualized as two and three-dimensional illustrations by using PyMOL version 2.4.1 and Discovery Studio Visualizer version 21.1.0.20298 respectively [24,25]. The two-dimensional chemical structures of these top ten hits were drawn by using MarvinSketch version 20.1 [26].

2.3 Prediction of Chemical, Pharmacokinetics and Mutagenic Characteristics of Hit Compounds

MCULE online platform provides the opportunity to predict various chemical features of the generated hit compounds. Drug-likeness score for the top ten hits were predicted by using Molsoft webserver [27]. Various pharmacokinetics and mutagenic characteristics for the top hits were predicted and calculated by using SwissADME and pkCSM webserver [28,29]. These webserver use predictive regression and molecular similarity to analyze molecules under investigation [30,31].

2.4 Molecular Dynamics (MD) Study

We have employed YASARA Dynamics version 20.12.24 to perform molecular dynamics (MD) simulation of the ligand-protein complex with the least binding energy pose [32]. The steps for molecular dynamics simulation study are similar to what we had followed in our previously published researches [21,33]. In summary, the MD protocol involves hydrogen bonds network optimization and a pKa prediction to fine-tune the protonation of residues at pH value equal to 7.4 [34]. NaCl was added with a concentration of 0.9%, an excess of either sodium or chloride ions were used to neutralize ligand-protein complex. To eliminate any possible clashes, steepest descent and simulated annealing minimizations were applied. The simulation period employed was 10 nanoseconds by using AMBER14 force field for solute, TIP3P for water, AM1BCC and GAFF2 for ligand [35–37]. The cutoff value for van der Waals (vdW) forces was 8 Angstrom, the default parameters were employed by AMBER [38]. By applying Particle Mesh Ewald algorithm, no cutoff value was used for electrostatic forces [39]. The motions equations were used as a multiple timestep of 1.25 and 2.5 femtoseconds

for bonded and non-bonded interactions respectively at a pressure of 1 atm and a temperature of 298K [40]. After assessment of root-mean-square deviation (RMSD) for the solute as a function of simulation period, the first 10 nanoseconds were regarded as the equilibration time and precluded from further analysis.

3. RESULTS AND DISCUSSION

A prediction of different chemical characteristics for the top ten hit compounds that were computationally screened against RBD crystal of SARS-CoV-2 spike protein can be seen in Table 1. In this table, the hit compounds were ranked according to their minimum binding energy to RBD crystal. According to Table 1, all these protein-protein interactions (PPIs) inhibitor candidates have a molecular weight greater than 400 g/ mol and a number of hydrogen bond accepters greater than 4. Regarding the prediction of partition coefficient logarithm (Log P), all the reported hits have Log P value greater than 4 with the exception of compounds 4, 9 and 10. The chemical structures for these top ten hits can be seen in Fig. 2 where all these compounds have more than 4 rings within their structures. Based on chemical data presented in Table 1 and Fig. 2, we can assess the adherence of these hit compounds to rule of four criteria.

In Table 2, various pharmacokinetics properties together with mutagenic potential are predicted and listed for the top ten hit compounds. These hits were ordered in Table 2 according to their predicted least binding energy as presented in this table. It is obvious that compounds 4, 9 and 10 have one violation for rule of four (RO4) criteria as seen in Table 2. The logarithm of partition coefficient (Log P) for these compounds is less than 4 as reported in Table 1. All the reported hits have a high predicted drug-likeness score with the exception of compounds 2, 3 and 8. Both compounds 1 and 6 were precluded from further analysis due to their anticipated poor water solubility. Additionally, compounds 4 and 10 may have a mutagenic capacity as predicted by AMES toxicity and therefore are excluded from any further examination. According to Table 2, only compounds 5 and 7 pass all the criteria for rule of four (RO4), have high drug-likeness score, possess moderate water solubility with no mutagenic capacity as indicated by predictive webserver. As such, only compounds 5 and 7 were considered for further evaluation of docking images and dynamics simulation.

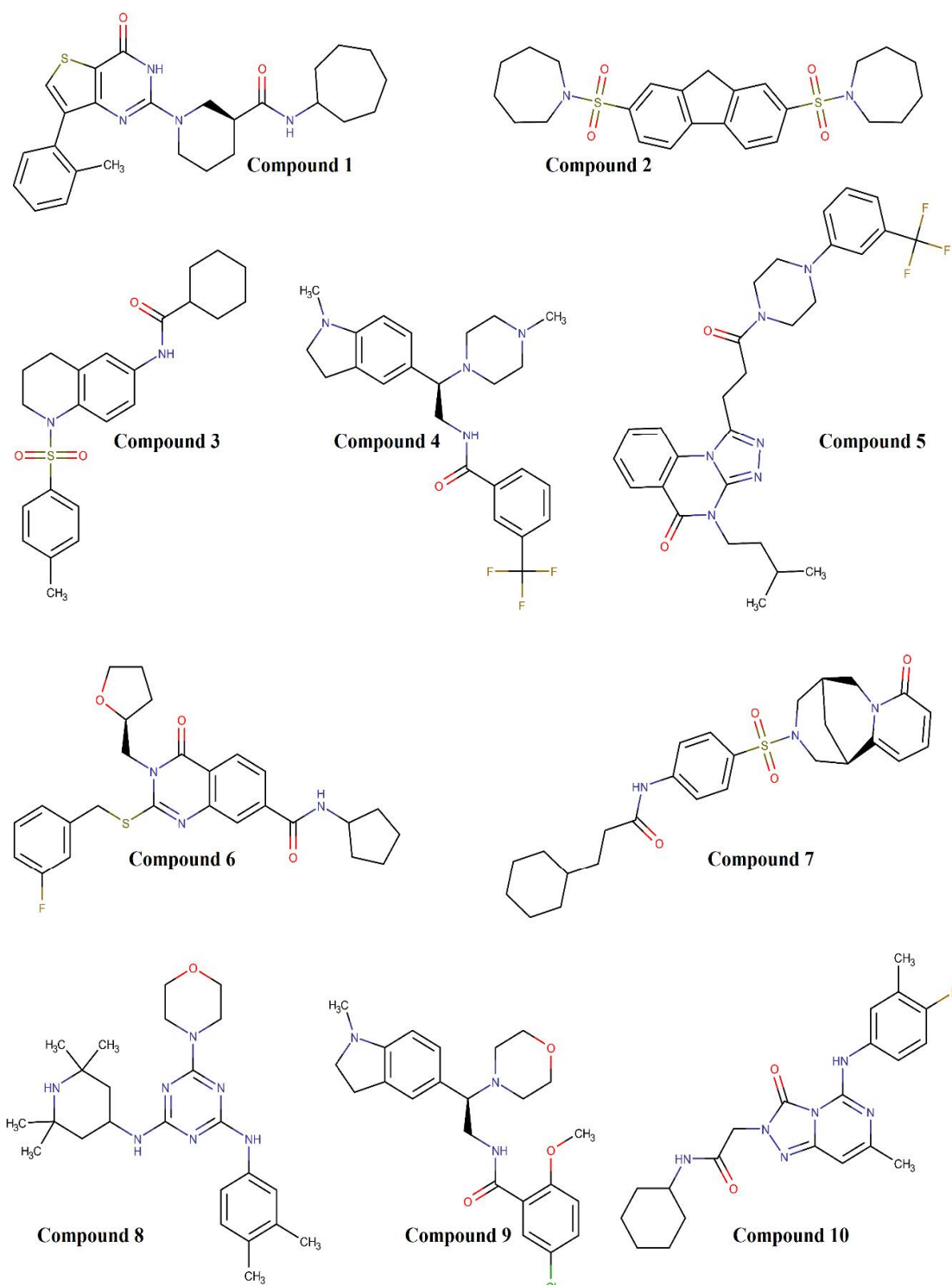


Fig. 2. Chemical structures of the top ten protein-protein interactions (PPIs) inhibitor candidates as screened virtually against receptor binding domain (RBD) of SARS-CoV-2 spike protein crystal. These candidates are ranked according to their minimum binding energy to RBD crystal

Table 1. Chemical characteristics of the top ten protein-protein interactions (PPIs) inhibitors that were virtually screened against receptor binding domain (RBD) crystal of SARS-CoV-2. These top hits were ranked according to their minimum binding energy to SARS-CoV-2 RBD crystal

Compound no	Molecular formula	M.W. (g/ mol)	Log P	TPSA (Å ²)	H-bond acceptors	H-bond donors
1	C ₂₆ H ₃₂ N ₄ O ₂ S	464.625	5.471	106.33	6	2
2	C ₂₅ H ₃₂ N ₂ O ₄ S ₂	488.667	6.425	91.52	6	0
3	C ₂₃ H ₂₈ N ₂ O ₃ S	412.547	5.874	74.86	5	1
4	C ₂₄ H ₂₉ F ₃ N ₄ O	446.508	3.748	38.82	5	1
5	C ₂₈ H ₃₁ F ₃ N ₆ O ₂	540.579	4.393	75.74	8	0
6	C ₂₆ H ₂₈ FN ₃ O ₃ S	481.584	5.070	98.52	6	1
7	C ₂₆ H ₃₃ N ₃ O ₄ S	483.624	5.047	96.86	7	1
8	C ₂₄ H ₃₇ N ₇ O	439.597	4.330	87.23	8	3
9	C ₂₃ H ₂₈ ClN ₃ O ₃	429.937	3.538	54.04	6	1
10	C ₂₁ H ₂₅ FN ₆ O ₂	412.460	3.303	93.32	8	2

M.W.: molecular weight; *Log P:* logarithm of partition coefficient; *TPSA:* topological polar surface area

Table 2. Predicted least binding energy, pharmacokinetic characteristics and mutagenic capacity of the top inhibitors for protein-protein interactions (PPIs) as screened against RBD crystal of SARS-CoV-2. These chemical compounds were arranged according to their predicted minimum binding energy to RBD crystal

No	Binding energy (Kcal/ mol)	RO4 violations	Drug-likeness score	Water solubility (mg/ ml)	Intestinal absorption (%)	VD _{ss} (L/Kg)	AMES toxicity
1	-8.7	0	1.16	7.43e-05(Poor)	92.95	3.43	No
2	-8.5	0	-0.88	6.39e-04(Moderate)	96.66	3.29	No
3	-8.5	0	0.52	4.76e-04(Moderate)	93.22	3.11	No
4	-8.1	1	1.88	3.36e-02(Moderate)	88.86	62.52	Yes
5	-8.0	0	1.23	1.03e-03(Moderate)	93.94	1.03	No
6	-7.8	0	1.00	3.37e-04(Poor)	96.27	2.55	No
7	-7.8	0	1.16	2.00e-03(Moderate)	96.28	1.50	No
8	-7.7	0	-0.49	5.71e-04(Moderate)	94.19	32.21	No
9	-7.6	1	1.76	4.77e-02(Soluble)	92.26	8.41	No
10	-7.6	1	0.62	5.66e-03(Moderate)	91.91	0.83	Yes

RO4: role of four; *VD_{ss}:* steady state volume of distribution.

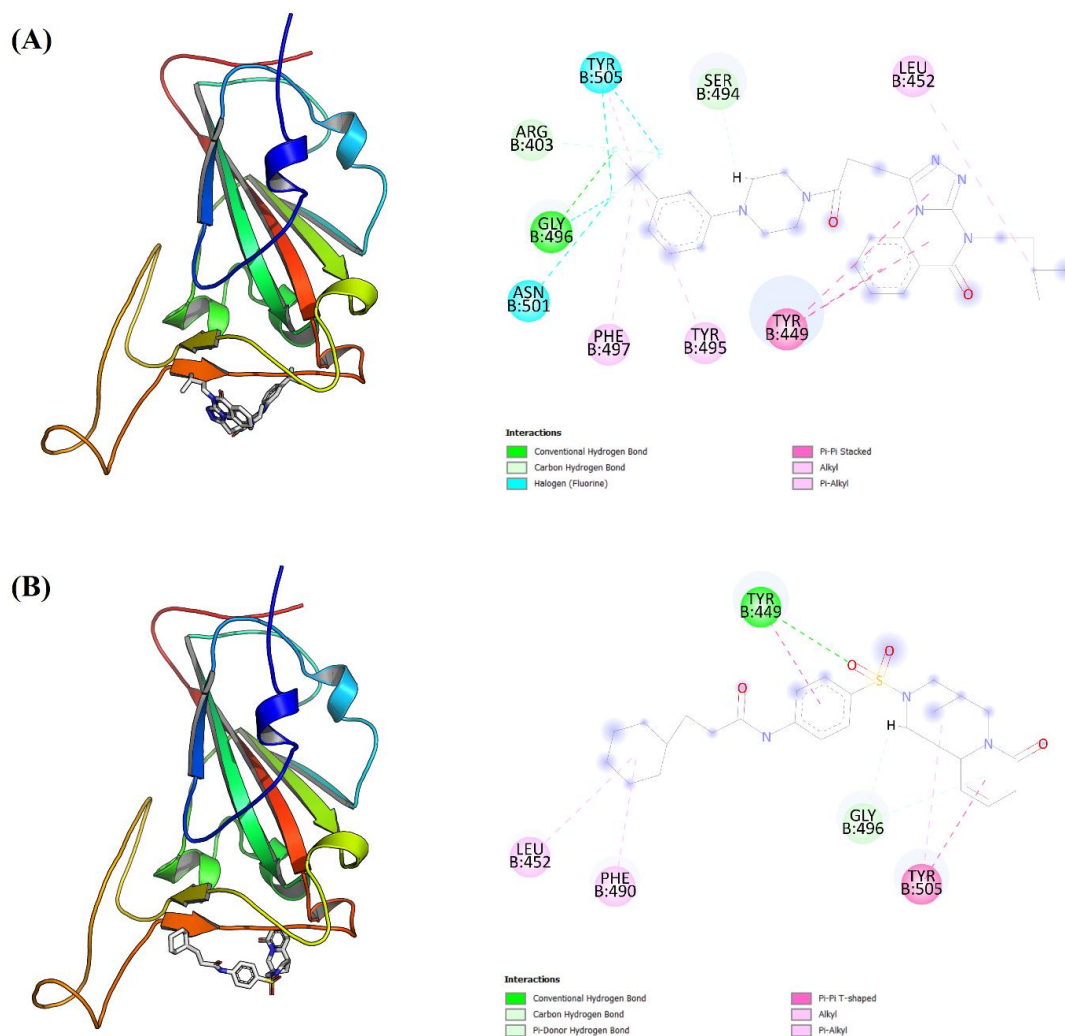


Fig. 3. Docking results of compound 5 and compound 7 against receptor binding domain of SARS-CoV-2 spike protein crystal are illustrated in three-dimensional and two-dimensional views as seen in (A) and (B) respectively. For each compound, only docking pose with least binding energy was considered here. For two-dimensional illustrations, colored discs represent amino acid residues in RBD interaction interface while dashed lines refer to interaction bonds

Careful examination of two and three-dimensional illustrations for compound 5 and 7 docking against RBD crystal with least binding energy pose, as presented in Fig. 3, reveal that both compounds may be involved in different kinds of chemical interactions with interface residues of RBD crystal. Of interest is the possible ability of compound 5 to form conventional hydrogen bond with Glycine 496 as seen in Fig. 3 (A). On the other hand, compound 7 may have the capacity to form conventional hydrogen bond with Tyrosine 449 as noticed in

Fig. 3 (B). Both Tyrosine 449 and Glycine 496 are considered interface residues of RBD crystal as can be seen in Fig. 1.

Finally, the results for compounds 5 and 7 molecular dynamics (MD) simulation were reported in both Fig. 4 and Fig. 5. By superposing the receptor on its reference structure, ligand proximity to RBD interface residues can be recorded as a function of simulation period as seen in Fig. 4. It is well-evident that compound 5 has moved away from

initial binding site by the end of simulation period as noticed in Fig. 4 (A), this may refer to weak interactions between compound 5 and RBD interface residues. On the other hand, Fig. 4 (B) shows that compound 7 can maintain a more constant distance from RBD interface as reported by root-mean-square deviation (RMSD) of ligand movement throughout 10 nanoseconds. This may indicate that compound 7 has stronger interactions with RBD crystal interface than does compound 5. Conformational changes RMSD of

compounds 5 and 7 can be seen in Fig. 5 (A) and (B) respectively. By superposing the ligand on its reference structure throughout simulation period, we can observe that the conformational changes RMSD for compounds 5 and 7 in Fig. 5 are consistent with ligand movement RMSD for these two compounds in Fig. 4. Based on these results, it is obvious that compound 7 may have more capacity than do compound 5 to bind interface residues of receptor binding domain for SARS-CoV-2 spike protein.

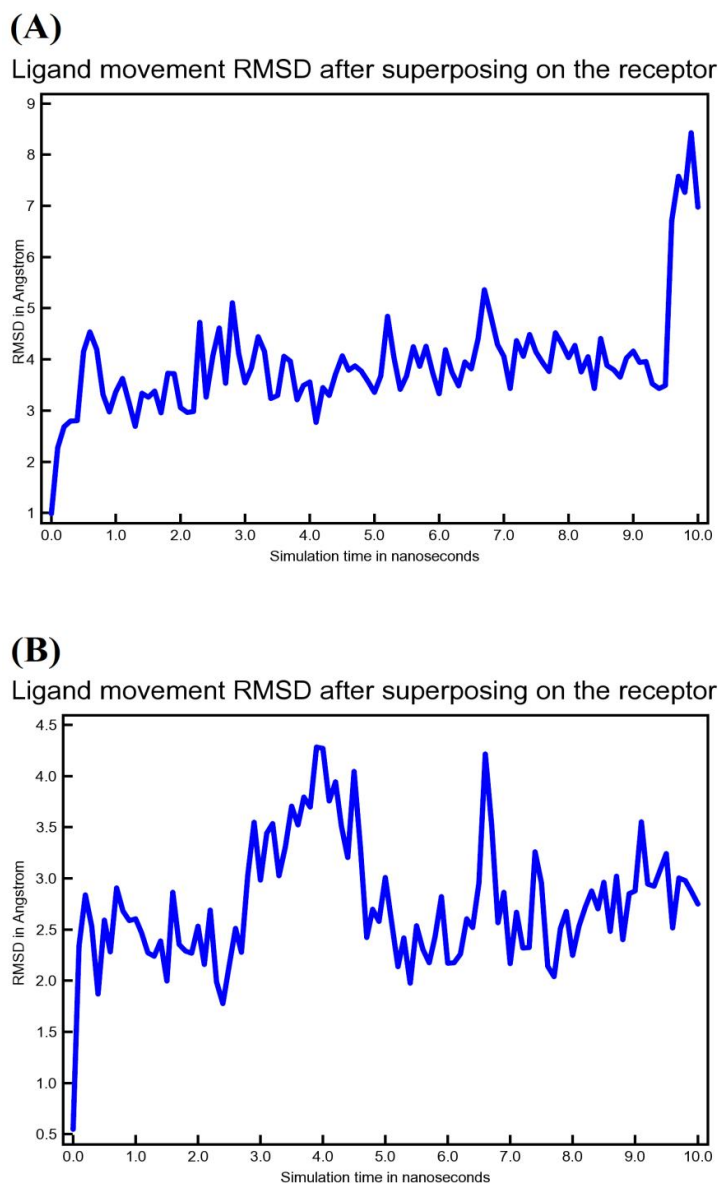


Fig. 4. Root-mean-square deviation (RMSD) of ligand movement as a function of simulation interval. Plot (A) is for compound 5 movement and plot (B) is for compound 7 movement

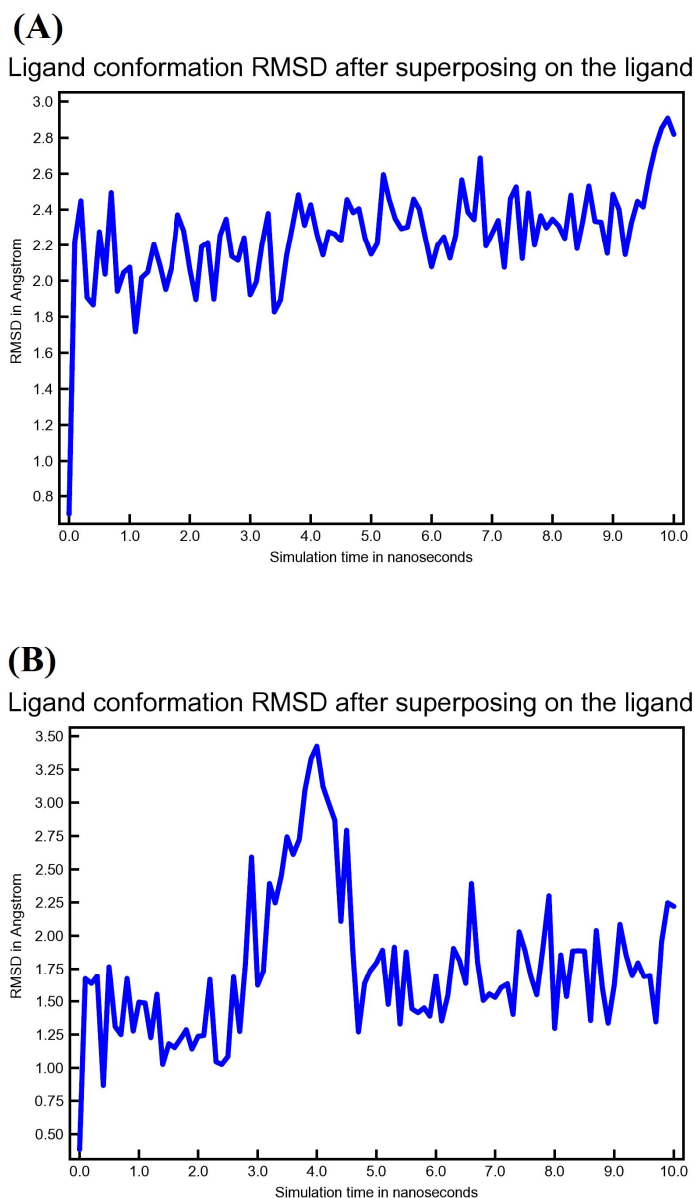


Fig. 5. Root-mean-square deviation (RMSD) of ligand conformational changes as a function of simulation interval. Plot (A) is for compound 5 conformational changes while plot (B) is for compound 7 conformational changes

4. CONCLUSION

We report that compound 7, with IUPAC name of 3-cyclohexyl-N-(4-[[[(1R,9R)-6-oxo-7,11-diazatricyclo [7.3.1.0^{2,7}] trideca-2,4-dien-11-yl] sulfonyl} phenyl) propanamide, may be able to interfere with interactions between RBD of SARS-CoV-2 spike protein and AC2 peptidase domain. Prediction of chemical and pharmacokinetics features along with outputs of

docking and molecular dynamics studies are supporting the possible capacity of compound 7 to inhibit cellular entry of SARS-CoV-2. However, the outputs of this virtual screening study may need further in vitro and in vivo evaluation.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per international standard or university standard ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Chauhan S. Comprehensive review of coronavirus disease 2019 (COVID-19). *Biomed J.* 2020;43(4):334–40.
2. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet.* 2020;395(10224):565–74.
3. Transmission of SARS-CoV-2: implications for infection prevention precautions. Accessed 27 Feb 2021. Available: <https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions>
4. Quesada JA, López-Pineda A, Gil-Guillén VF, Arriero-Marín JM, Gutiérrez F, Carratala-Munuera C. Incubation period of COVID-19: A systematic review and meta-analysis. *Rev Clínica Española.* 2021; 221(2):109–17.
5. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA - J Am Med Assoc.* 2020;324(8):782–93.
6. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. *Int J Infect Dis.* 2020;101:138–48.
7. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2021; 384(8):693–704.
8. Gozzo L, Viale P, Longo L, Vitale DC, Drago F. The Potential role of heparin in patients with COVID-19: Beyond the anticoagulant effect. A review. *Front Pharmacol.* 2020;11.
9. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 — final report. *N Engl J Med.* 2020; 383(19):1813–26.
10. COVID-19 vaccines. Accessed 27 Feb 2021. Available: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines>
11. Belete TM. Review on up-to-date status of candidate vaccines for covid-19 disease. *Infect Drug Resist.* 2021;14:151–61.
12. Han Q, Lin Q, Jin S, You L. Coronavirus 2019-nCoV: A brief perspective from the front line. *J Infect.* 2020;80(4):373–7.
13. Baig MS, Alagumuthu M, Rajpoot S, Saqib U. Identification of a potential peptide inhibitor of SARS-CoV-2 targeting its entry into the host cells. *Drugs R D.* 2020; 20(3):161–169.
14. Morelli X, Bourgeas R, Roche P. Chemical and structural lessons from recent successes in protein-protein interaction inhibition (2P2I). *Curr Opin Chem Biol.* 2011;15(4):475–81.
15. PPI Focused Libraries by Ligand-based Approach. Accessed 28 Feb 2021. Available: <https://lifechemicals.com/screening-libraries/targeted-and-focused-screening-libraries/ppi-libraries/ppi-focused-library>
16. RCSB PDB - 6LZG: Structure of novel coronavirus spike receptor-binding domain complexed with its receptor ACE2. Accessed 05 Mar 2021. Available: <https://www.rcsb.org/structure/6LZG>
17. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell.* 2020;181(4):894–904.e9.
18. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera - A visualization system for exploratory research and analysis. *J Comput Chem.* 2004;25(13):1605–1612.
19. MCULE. Accessed 05 Mar 2021. Available: <https://mcule.com/>
20. Odhar HA, Rayshan AM, Ahjel SW, Hashim AA, Albeer AAMA. Molecular docking enabled updated screening of the matrix protein VP40 from Ebola virus with millions of compounds in the MCULE database for potential inhibitors. *Bioinformatics.* 2019;15(9):627–632.

21. Odhar HA, Ahjel SW, Albeer AAMA, Hashim AF, Rayshan AM, Humadi SS. Molecular docking and dynamics simulation of FDA approved drugs with the main protease from 2019 novel coronavirus. *Bioinformation*. 2020;16(3): 236–244.
22. Trott O, Olson AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem*. 2009;31(2):455-461.
23. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, et al. AutoDock4 and AutoDock Tools 4: Automated docking with selective receptor flexibility. *J Comput Chem*. 2009;30(16): 2785–2791.
24. PyMOL. Accessed 05 Mar 2021. Available:<https://pymol.org/2/>
25. Free Download: BIOVIA Discovery Studio Visualizer - Dassault Systèmes. Accessed 05 Mar 2021. Available:<https://discover.3ds.com/discovery-studio-visualizer-download>
26. Marvin ChemAxon. Accessed 05 Mar 2021. Available:<https://chemaxon.com/products/marvin>
27. Molsoft LLC. Drug-likeness and molecular property prediction. Accessed 05 Mar 2021. Available:<https://molsoft.com/mprop/>
28. SwissADME. Accessed 05 Mar 2021. Available:<http://www.swissadme.ch/>
29. pkCSM. Accessed 05 Mar 2021. Available:<http://biosig.unimelb.edu.au/pkcs m/prediction>
30. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep*. 2017;7.
31. Pires DEV, Blundell TL, Ascher DB. pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *J Med Chem*. 2015;58(9):4066–4072.
32. Krieger E, Vriend G. YASARA View - molecular graphics for all devices - from smartphones to workstations. *Bioinformatics*. 2014;30(20):2981–2.
33. Odhar HA, Ahjel SW, Humadi SS. Towards the design of multiepitope-based peptide vaccine candidate against SARS-CoV-2. *bioRxiv*. 2020; 2020.07.07.186122.
34. Krieger E, Dunbrack RL, Hoof RWW, Krieger B. Assignment of protonation states in proteins and ligands: Combining pK a prediction with hydrogen bonding network optimization. *Methods Mol Biol*. 2012;819:405–421.
35. Maier JA, Martinez C, Kasavajhala K, Wickstrom L, Hauser KE, Simmerling C. ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. *J Chem Theory Comput*. 2015;11(8):3696–3713.
36. Wang J, Wolf RM, Caldwell JW, Kollman PA, Case DA. Development and testing of a general Amber force field. *J Comput Chem*. 2004;25(9):1157–1174.
37. Jakalian A, Jack DB, Bayly CI. Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. *J Comput Chem*. 2002;23(16):1623–1641.
38. Hornak V, Abel R, Okur A, Strockbine B, Roitberg A, Simmerling C. Comparison of multiple amber force fields and development of improved protein backbone parameters. *Proteins Struct Funct Genet*. 2006;65(3):712–725.
39. Essmann U, Perera L, Berkowitz ML, Darden T, Lee H, Pedersen LG. A smooth particle mesh Ewald method. *J Chem Phys*. 1995;103(19):8577–8593.
40. Krieger E, Vriend G. New ways to boost molecular dynamics simulations. *J Comput Chem*. 2015;36(13):996–1007.

© 2021 Odhar et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:
 The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/66801>