JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

Molecular Docking Interaction of Medicines Binding to COVID-19 Proteins

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Abstract: In late 2019, in Wuhan, China, a new human coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first appeared. This virus caused the respiratory ailment known as coronavirus disease 2019 (COVID-19), which spread quickly throughout the world. Researchers from all over the world are working feverishly to comprehend SARS-CoV-2 and explore the pathophysiology of this illness to identify viable therapeutic drug candidates and treatments. This research is part of our ongoing search for an effective antiviral medication to combat this devastating illness, which necessitates work in medicinal chemistry. Every day, a sizable number of people die from the terrible disease COVID-19. This research looked at using docking theoretical calculations for dealing with the docking between medicines with proteins. Nine compounds of medicines named Aminoglutethimide, 4-aminosalicylic acid, Felbamate, Hydroflumethiazide, Methazolamide, Modafinil, Nepafenac, Oxcarbazepine and Trichlormethiazide are used that are commonly active groups like amino group, hydroxyl, and ketone in their conformation structures. Two inhibitions of proteins in the SARS-CoV-2 virus (COVID-19) are applied (6xbg and 6xfn) for docking with nine medicines depending on the software of the Molecular operating environment package (MOE). The docking score was found to be that trichlormethiazide had a more stable value (-6.2955) and (-6.5462) with (6xbg) and (6xfn) proteins respectively.

Keywords: SARS-CoV-2, COVID-19, Docking, Theoretical calculations, MOE.

Submitted: April 12, 2023. **Accepted:** October 31, 2023.

Cite this: Ibrahim AA, Sulliman EA, Ibrahim MA. Molecular Docking Interaction of Medicines Binding to COVID-19 Proteins. JOTCSA. 2024;11(1):261-8.

DOI: https://doi.org/10.18596/jotcsa.1281563

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1. INTRODUCTION

The World Health Organization (WHO) classified a new illness in Wuhan City, China, as a pandemic in March 2020. The coronavirus associated with this pandemic, COVID-19, was proposed as a new variety of SARS-CoV-2 (1). More than one million patients were suffering death and about 40 million have been infected (2-4). Computational features (5) provide new ideas for common medicines used to combat newer coronaviruses. Through molecular docking (6), a virtual screening approach was used to discover the active site of the viral protease for the binding of numerous natural chemicals (7).

To find a new treatment for COVID-19 by putting forth a mechanism for these interactions, a docking study of coumarin derivatives with chloroquine was carried out (8). There is no effective treatment for COVID-19 at this yet (9). The search for novel medications, particularly those derived from natural plant sources (10), has enormous potential. UV rays, traumas, and bacterial and fungal poisons can all trigger a reaction. Anti-inflammatory, antitumoral, and antiviral agents are various biological functions in human extraction from plants (11-13).

Utilizing molecular docking software, the study of drug interactions with proteins was used to approach drug design and evolution (14,15). SARS-CoV-2-related proteins have been identified as potential therapeutic targets in numerous theoretical investigations, and hundreds of dockings have been conducted with different drugs (16,17).

The best efforts of scientists are being made in this direction. discovery of a chemical to combat this virus, but the outcomes so far are very limited. Since it takes a while, starting from scratch with a new medication in this situation is not a good idea. It

costs a lot of money and time to create a new molecule. COVID-19 is resistant to several known medicines (5, 18). The Food and Drug Administration (FDA) authorized malaria medicine hydroxyl-chloroquine was investigated as a treatment for SARS-CoV-2. Previous research has shown that chloroquine and hydroxychloroquine (19) can suppress the coronavirus (COVID-19) by altering the pH at the cell membrane's surface (20, 21).

Heterocyclic molecules are known as antiviral drugs and are the subject of extensive research for potential medical applications (5, 22). To explore the efficiency of the medicines as COVID-19 inhibitors, comparative research comparing pharmaceuticals with FDA approval and hydroxychloroquine antiviral treatments against a wide range of RNA viruses has been established (15).

Coronaviruses, positive sense-RNA viruses that reproduce in the cytoplasm, are present in infected human cells. A sophisticated replication machinery component that regulates their replication is made up of at least 16 non-structural proteins (23, 24).

COVID-19 was studied in the human body (25), while different types of computations, including pm3, am1, and hf at the basis set (sto-3g), were used to conceptually analyze the medications. Entropy, Gibbs free energy, HOMO, total energy, and LUMO were calculated among other physicochemical data. For the interaction of drugs with various proteins, docking studies were used (26).

Aminoglutethimide is a drug that has been used to treat Cushing's syndrome, breast cancer, prostate cancer, and seizures. While 4-aminosalicylic acid is mainly used as an antibiotic to treat tuberculosis. In particular, it is used in conjunction with other antituberculosis drugs to treat active drug-resistant tuberculosis.

Felbamate is an anticonvulsant that is applied to epilepsy patients. It is used to treat Lennox-Gas taut syndrome-related partial and generalized seizures in children as well as partial seizures in adults, both with and without generalization. Hydroflumethiazide is a thiazide diuretic used to treat liver cirrhosis, congestive heart failure, and hypertension-related edema.

Methazolamide is recommended for the management of elevated intraocular pressure (IOP) in both secondary and chronic open-angle glaucoma. Modafinil is a central nervous system (CNS) stimulant drug used to treat obstructive sleep apnea, narcolepsy, and shift work sleep disorder-related insomnia.

Nepafenac is a nonsteroidal anti-inflammatory drug (NSAID) used to treat cataract surgery-related pain and inflammation. Oxcarbazepine is a drug used for the treatment of epilepsy. It is used to treat both focal and generalized seizures in epilepsy. Trichlormethiazide is typically used to treat hypertension and edema, including those brought on by hepatic cirrhosis, cardiac failure, and cortico-steroid therapy.

2. COMPUTATIONAL METHODS

A docking study was carried out to optimize the medicines with proteins. Structures of the proteins have been chosen from the protein database website (PDB) having the code (6xbg and 6xfn) (27). Water structures, and alternative molecules, were left out of the protein's 3D coordinate information. These proteins were separated from other molecules such as water, alternative compounds, and tiny proteins with a small number of amino acids. These proteins were afterward re-corrected and re-arranged automatically after the hydrogen atoms in the structure were added.

Chem-Bio Office 3D (version 17.1) was used to create the pharmaceutical molecules. The docking software (MOE) (version 2015) was used to characterize all of the ligands and receptors. Simulation of docking was carried out by selecting the active sites of the proteins to arrive at a final optimization to find a configuration that was more stable and had lower steric hindrance.

Using an Intel Core (i7-4810) laptop computer with (8 GB) of RAM and Microsoft Windows 10 Pro as the operating system, docking for ligand and receptor was computed.

3. RESULTS AND DISCUSSION

The docking investigation was used to predict the docking interaction of numerous medications, whose formulas are shown in Figure 1, with various proteins. The activity of these proteins in the SAR-Cov2 virus was taken into consideration when they were chosen.

3.1. Docking of (6xbg)

This protein has (2407) atoms and (300) residues in its structure. Figure 1 shows the complete formula, which comprises 1515 carbon atoms, 405 oxygen atoms, and 27 sulfur atoms (2). There are a lot of active functional groups in these proteins, notably nitrogen, and oxygen.

3.1.1. Docking with Medicines

The binding score energy of (6xbg) protein was calculated. As indicated in Table (1), we selected the optimal location of the protein to interact with different medications to determine the best docking. The (E-9, E-7, E-4, E-6, E-3, E-1, E-5, E-8, and E-2) were discovered to have energy score values of -6.2955, -6.1897, -6.1514, -6.0182, -5.8292, -5.6303, -5.6060, -5.5381, and -4.4638. So, it's clear that every drug is superior to E-9.

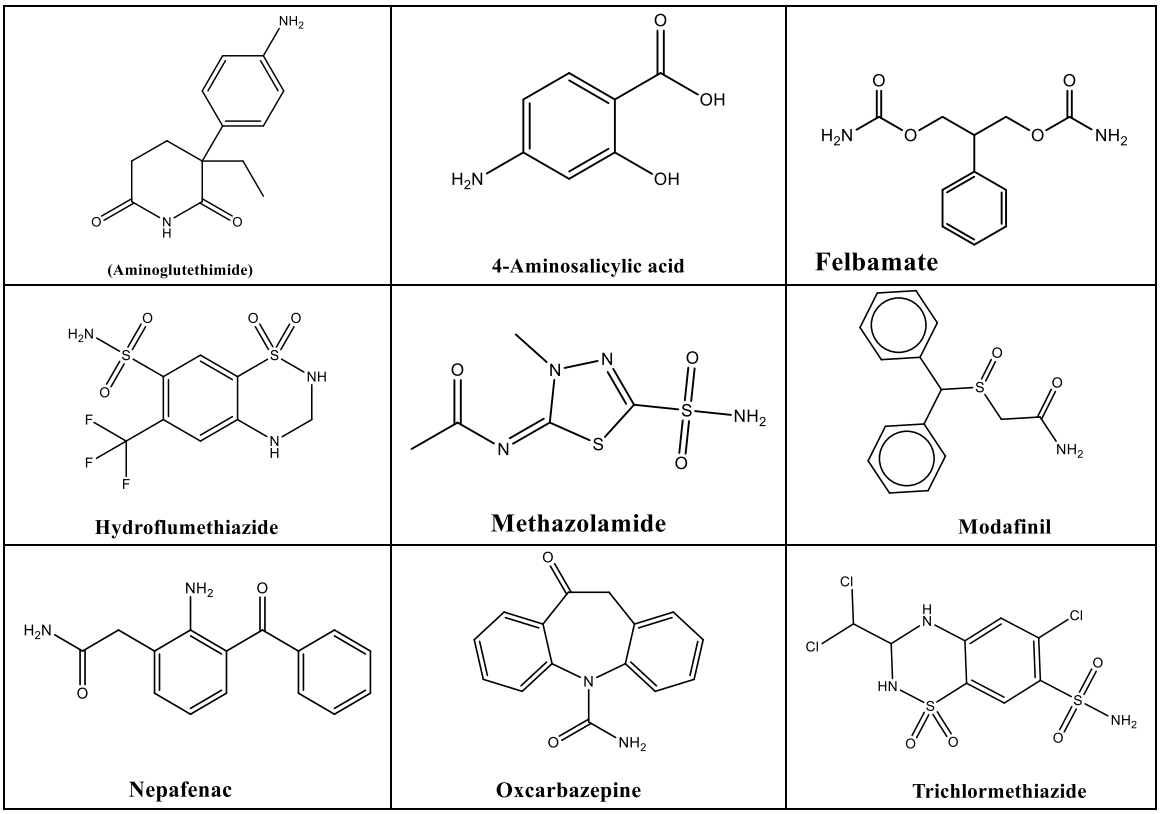


Figure 1: Pharmaceutical substances' molecular structure.

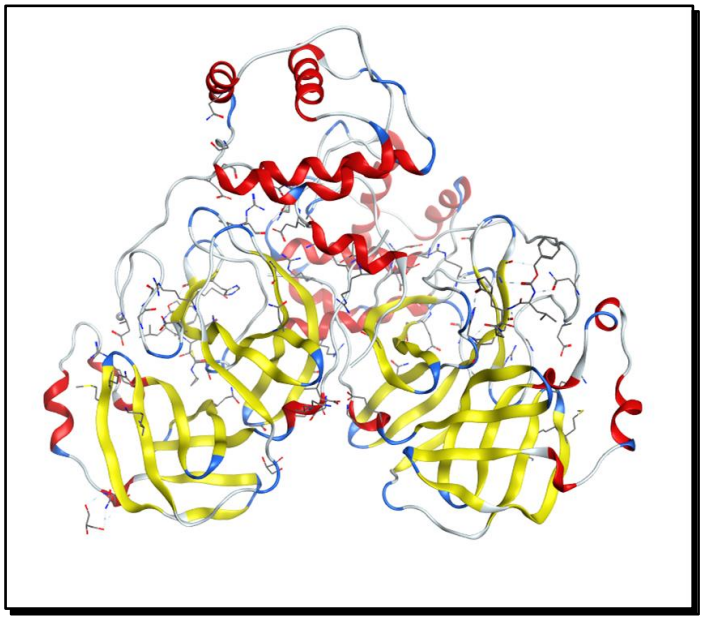


Figure 2: The configuration of (6xbg) protein.

Table 1: Score values for docking of (6xbg) protein with medicines.

Comp. No.	Medicines	Score values
E-1	Aminoglutethimide	-5.6303
E-2	4-Aminosalicylic acid	-4.4638
E-3	Felbamate	-5.8292
E-4	Hydroflumethiazide	-6.1514
E-5	Methazolamide	-5.6060
E-6	Modafinil	-6.0182
E-7	Nepafenac	-6.1897
E-8	Oxcarbazepine	-5.5381
E-9	Trichlormethiazide	-6.2955

When compared to other medicines, trichlormethiazide (-6.2955) had a more stable value, but 4-aminosalicylic acid (-4.4638) did not.

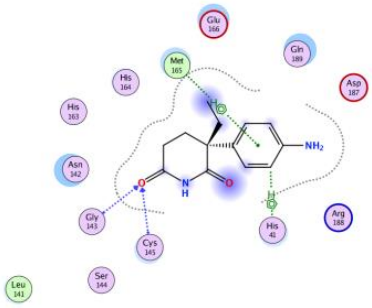
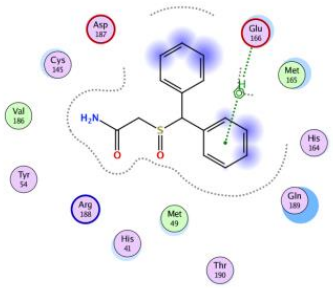
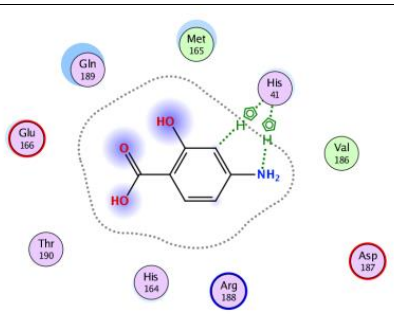
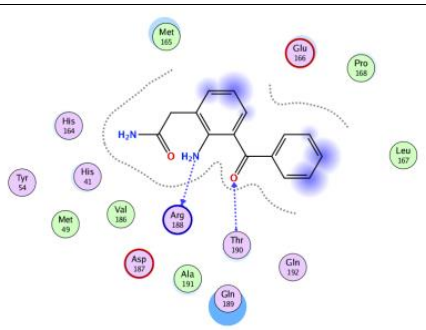
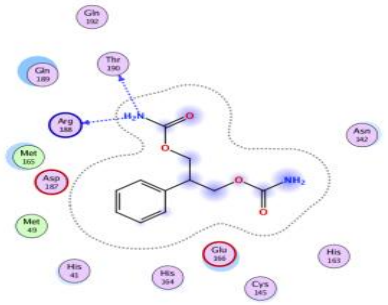
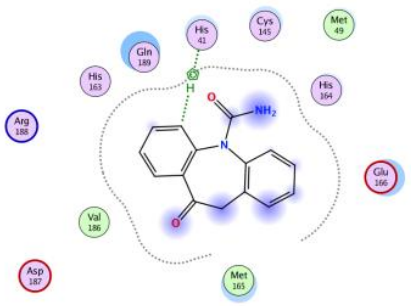
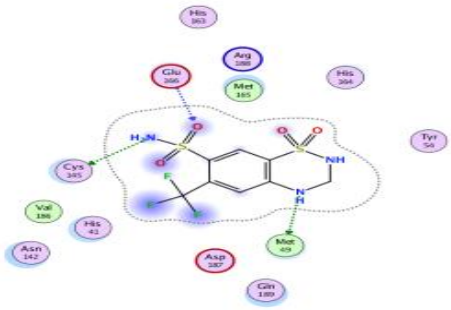
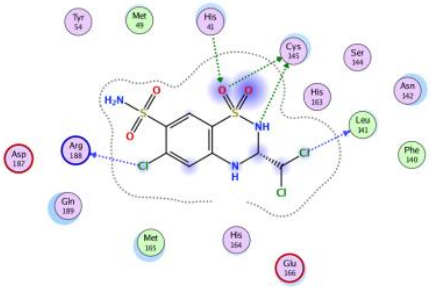
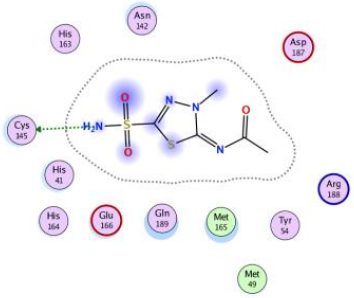
Comp. No.	Docking with Protein	Comp. No.	Docking with Protein
E-1		E-6	
E-2		E-7	
E-3		E-8	
E-4		E-9	
E-5			

Figure 3: Medicines docking with the (6xbg) protein.

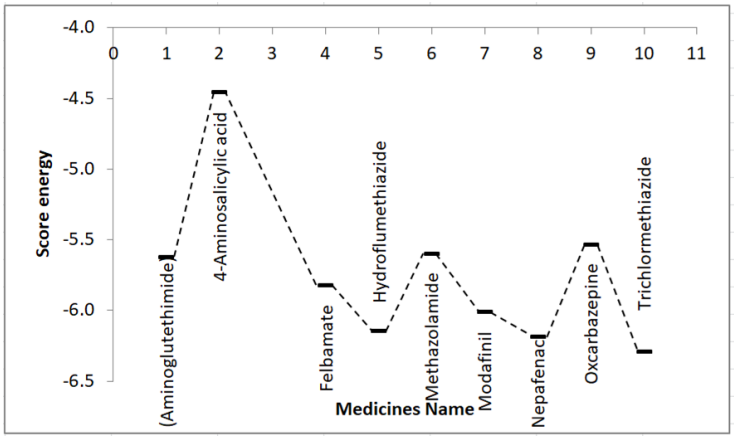


Figure 4: Drug scores at (6xbg) protein.

Various amino acid groups surround the medication (trichlormethiazide). A (His 41) and (Cys 145) intermolecular hydrogen bond linked the active polar site between the medication and the protein, as did (Leu 141) and (Arg188) via free electrons in chlorine as illustrated in Figure (3). By (π) aromatic system, the medication (4-Aminosalicylic acid) came into touch with the amino acid group (His 41).

There are three chlorine atoms in the formula of the medication (Trichlormethiazide), which makes it unique. (NH_2, =O) have active groups, however, this molecule has a higher polarity and is more active. There are a few reasons why Trichlormethiazide was chosen above the others as a medication name.

3.2. Docking of (6xfn)

This protein has around 304 residues and 23488 atoms. As illustrated in Figure 5, the entire formula contained 1486 carbon atoms, 398 nitrogen atoms, 441 oxygen atoms, and 23 sulfur atoms.

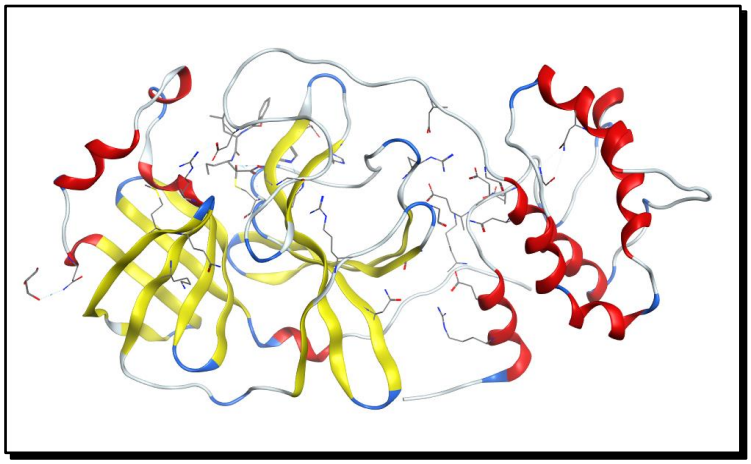


Figure 5: The configuration of (6xfn) protein.

3.2.1. Docking with Medicines

Following that, we chose the optimal location of the protein to interact with various medications to describe the best docking, as indicated in the table below.

Table 2: Score values for docking of (6xfn) protein with medicines.

Comp. No.	Medicines	Score values
E-1	Aminoglutethimide	-5.5095
E-2	4-Aminosalicylic acid	-4.5654
E-3	Felbamate	-5.6109
E-4	Hydroflumethiazide	-5.9720
E-5	Methazolamide	-5.5635
E-6	Modafinil	-5.6988
E-7	Nepafenac	-6.1798
E-8	Oxcarbazepine	-5.5411
E-9	Trichlormethiazide	-6.5462

As indicated in Figure 7, the drug Trichlormethiazide requires a more stable value -6.5462, but the medicine 4-Aminosalicylic acid requires a less stable value -4.5654.

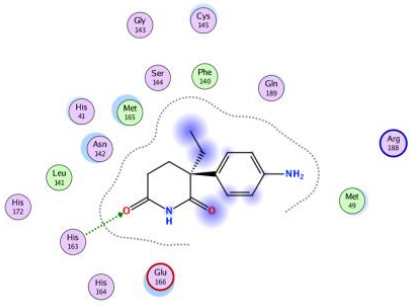
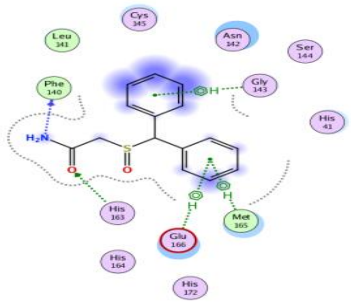
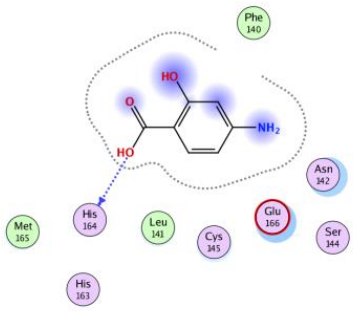
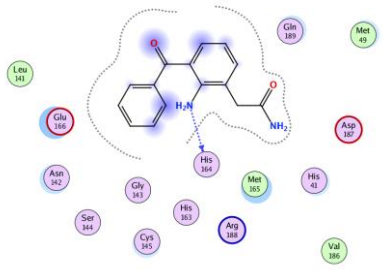
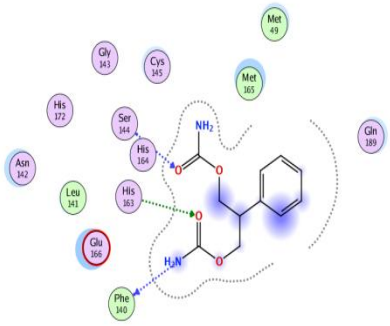
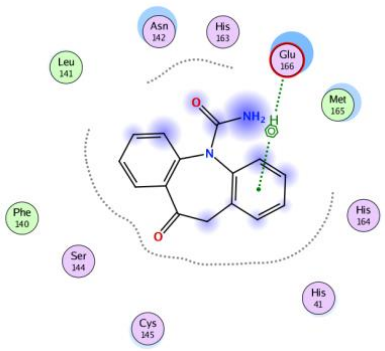
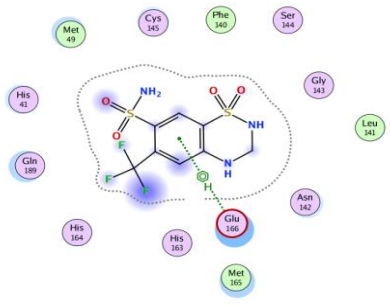
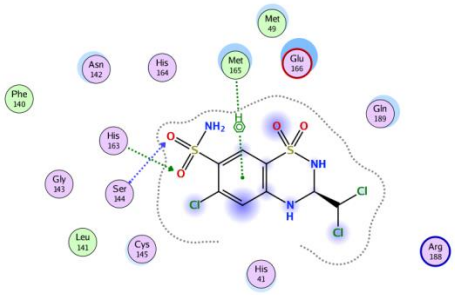
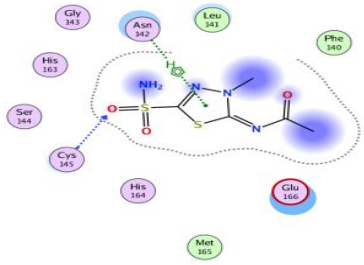
Comp No.	Docking with Protein	Comp No.	Docking with Protein
E-1		E-6	
E-2		E-7	
E-3		E-8	
E-4		E-9	
E-5			

Figure 6: Medicines docking with the (6xfn) protein.

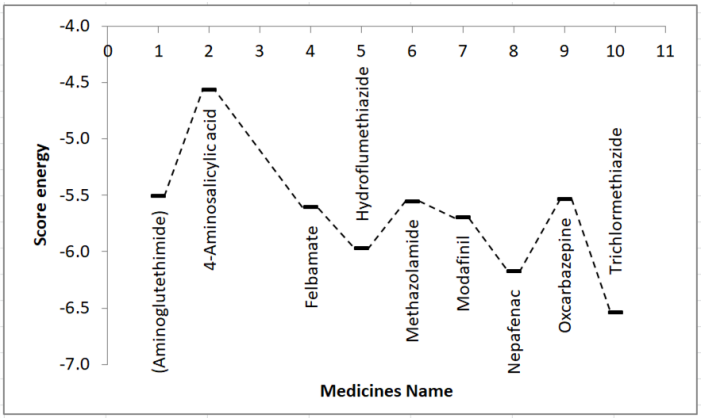


Figure 7: Drug scores at (6xfn) protein.

Many amino acid molecules plagued trichlormethiazide therapy. By an intermolecular hydrogen bond, the active site was close to the protein Met 165. In ketone, free electrons were linked to His 163 and Ser 144. Finally, a hydrogen atom joined 4-aminosalicylic acid medication of His 164.

As a result, the medication Trichlormethiazide has three chlorine atoms in its formula, making it more polar and active than other compounds, in addition to having active groups like NH_2, =O in its formula structure. As a result of these factors, the medication name Trichlormethiazide was more stable than the others.

Figure 8 shows the comparison of two medications Trichlormethiazide and 4-aminosalicylic acid and two proteins. In comparison to 6xfn, we may infer that Trichlormethiazide was more active binding docking and more stable compared with 6xbg. In comparison to other medicines, 4-aminosalicylic acid was less stable.

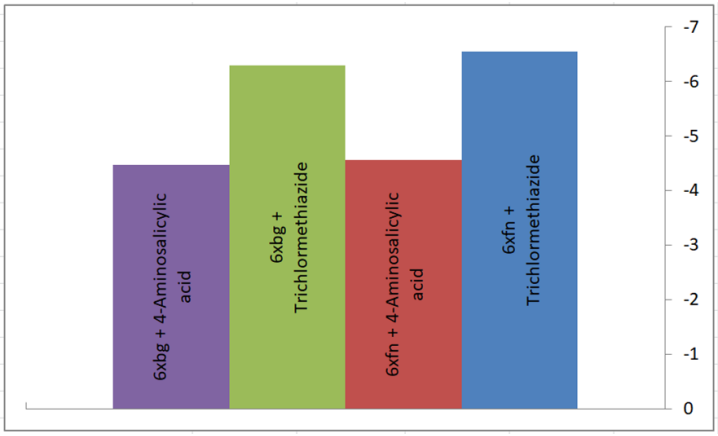


Figure 8: Score comparison of medications containing proteins.

4. CONCLUSION

This study aims to measure the binding affinity of the active compounds within the target protein that are involved in the virus' entry and replication mechanisms, and consequently in the in-silico process of the virus' host cell maturation. The docking results revealed a variety of drug-protein binding interactions, some of which were advantageous. The COVID-19 in complex with the inhibitors exhibited high-affinity interactions with the antiviral medications aminoglutethimide, 4-aminosalicylic acid, Felbamate, hydroflumethiazide, methazolamide, modafinil, nepafenac, oxicarbazepine, and trichlormethiazide. The docking findings revealed that medication Trichlormethiazide was the most active against the proteins 6xfn and 6xbg with values of -6.5462 and -6.2955, respectively, in comparison to others. With values of -4.5654 and -4.4638, medication 4-Aminosalicylic acid had reduced docking binding with the preceding proteins.

5. ACKNOWLEDGMENTS

The Department of Chemistry, Faculty of Sciences, University of Mosul is acknowledged by the authors for its support and cooperation.

6. REFERENCES

1. World Health Organization (WHO). Coronavirus Disease (COVID-19) Situation Reports [Internet]. 2020. Available from: <URL>.

2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet [Internet]. 2020 Feb 15;395(10223):470–3. Available

from: <URL>.

3. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci [Internet]. 2020 Mar 21;63(3):457–60. Available from: <URL>.

4. Mali SN, Pratap AP, Thorat BR. The Rise of New Coronavirus Infection-(COVID-19): A Recent Update. Eurasian J Med Oncol [Internet]. 2020;4(1):35–41. Available from: <URL>.

5. Hagar M, Chaieb K, Parveen S, Ahmed HA, Alnoman RB. N-alkyl 2-pyridone versus O-alkyl 2-pyridol: Ultrasonic synthesis, DFT, docking studies and their antimicrobial evaluation. J Mol Struct [Internet]. 2020 Jan 5;1199:126926. Available from: <URL>.

6. Alnoman RB, Parveen S, Hagar M, Ahmed HA, Knight JG. A new chiral boron-dipyrromethene (BODIPY)-based fluorescent probe: molecular docking, DFT, antibacterial and antioxidant approaches. J Biomol Struct Dyn [Internet]. 2020 Dec 11;38(18):5429–42. Available from: <URL>.

7. Liu C, Ma Y, Zhao J, Nussinov R, Zhang Y-C, Cheng F, et al. Computational network biology: Data, models, and applications. Phys Rep [Internet]. 2020 Mar 3;846:1–66. Available from: <URL>.

8. Ibrahim AA, Yahya OM, Ibrahim MA. Theoretical Prediction of Possible Drug Treatment of COVID-19 using Coumarins Containing Chloroquine Moeity. Asian J Chem [Internet]. 2020 Dec 7;32(12):3120–6. Available from: <URL>.

9. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med [Internet]. 2020 May 4;35(5):1545–9. Available from: <URL>.

10. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol [Internet]. 2020 May 3;92(5):479–90. Available from: <URL>.

11. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential Inhibitor of COVID-19 Main Protease (Mpro) From Several Medicinal Plant Compounds by Molecular Docking Study. Preprints [Internet]. 2020 Mar 13;1–14. Available from: <URL>.

12. Khan SA, Zia K, Ashraf S, Uddin R, Ul-Haq Z. Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 *via* integrated computational approach. J Biomol Struct Dyn [Internet]. 2021 May 3;39(7):2607–16. Available from: <URL>.

13. Wahedi HM, Ahmad S, Abbasi SW. Stilbene-based natural compounds as promising drug candidates against COVID-19. J Biomol Struct Dyn [Internet]. 2020 May 12;39(9):3225–34. Available from: <URL>.

14. Jorgensen WL. The Many Roles of Computation in Drug Discovery. Science (80-) [Internet]. 2004 Mar 19;303(5665):1813–8. Available from: <URL>.

15. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res [Internet]. 2020 Mar 4;30(3):269–71. Available from: <URL>.

16. Wang J. Fast Identification of Possible Drug Treatment of Coronavirus Disease-19 (COVID-19) through Computational Drug Repurposing Study. J Chem Inf Model [Internet]. 2020 Jun 22;60(6):3277–86. Available from: <URL>.

17. Tallei TE, Tumilaar SG, Niode NJ, Fatimawali, Kepel BJ, Idroes R, et al. Potential of Plant Bioactive Compounds as SARS-CoV-2 Main Protease (Mpro) and Spike (S) Glycoprotein Inhibitors: A Molecular Docking Study. Riganti C, editor. Scientifica (Cairo) [Internet]. 2020 Dec 23;2020:6307457. Available from: <URL>.

18. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med [Internet]. 2020 Mar 5;382(10):929–36. Available from: <URL>.

19. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell [Internet]. 2020 Apr 16;181(2):271–80. Available from: <URL>.

20. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents [Internet]. 2020 May 1;55(5):105938. Available from: <URL>.

21. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis [Internet]. 2020 Jul 28;71(15):732–9. Available from: <URL>.

22. Gong H-H, Addla D, Lv J-S, Zhou C-H. Heterocyclic Naphthalimides as New Skeleton Structure of Compounds with Increasingly Expanding Relational Medicinal Applications. Curr Top Med Chem [Internet]. 2016 Sep 26;16(28):3303–64. Available from: <URL>.

23. den Boon JA, Diaz A, Ahlquist P. Cytoplasmic Viral Replication Complexes. Cell Host Microbe [Internet]. 2010 Jul 22;8(1):77–85. Available from: <URL>.

24. Hackbart M, Deng X, Baker SC. Coronavirus endoribonuclease targets viral polyuridine sequences to evade activating host sensors. Proc Natl Acad Sci [Internet]. 2020 Apr 7;117(14):8094–103. Available from: <URL>.

25. Kareem AM, Al-Azzawi SN. Comparison Between Deterministic and Stochastic Model for Interaction (COVID-19) With Host Cells in Humans. Baghdad Sci J [Internet]. 2022 Oct 23;19(5):1140–7. Available from: <URL>.

26. Ibrahim AA. A Theoretical Study of the Docking of Medicines with some Proteins. Baghdad Sci J [Internet]. 2023 Apr 1;20(2):483–91. Available from: <URL>.

27. https://www.rcsb.org/