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Investigation of COVID-19 By Theoretical Docking of Medicines With Two Proteins

Ammar A. Ibrahim [a]*, Mohammed F. Haddad[b], Maher A. Ibrahim [c], Ali W. Kasim [d]

[a] *Department of Chemistry, College of Science, University of Mosul, IRAQ*
[b] *Northern Technical University, IRAQ*
[c] *Department of Biochemistry, College of Medicine, University of Mosul, IRAQ*
[d] *Ministry of Health, IRAQ*

Abstract

This study examined the docking of two inhibition for SARS-Cov-2 virus (or COVID-19) these proteins are (6wtt and 6xa4) with nine pharmaceutical compounds (Aminoglutethimide, 4-Aminosalicylic acid, Felbamate, Hydroflumethiazide, Modafinil, Nepafenac, Oxcarbazepine, and Trichlormethiazide) which are used in the general human's life. These pharmaceuticals have different active groups in the structure conformation like (-NH2) and (-OH). Docking was applied the investigate the interaction between these medicines with the proteins using Molecular Operating Environment software (MOE). The goal of this study was to find a novel drug that docked with some proteins and was regarded to be an effective therapy for COVID-19.
Keywords: COVID-19, Docking, Proteins, ligand-receptor interaction

1. Introduction

Coronavirus pandemic was appeared and characterized by humans disease in China especially in Wuhan city in December 2019. Worldwide, more than 40 million persons were infected, and one million died from COVID-19. For this situation, the World health organization (WHO) describes COVID-19 as a pandemic[1-4].

COVID-19 infection may be a new version of SARS-CoV-2 which showed up as stronger, fiercer, and highest death rate[5,6]. So, this widespread has the same indications as flu. Tiredness, headache, fever, dry cough, and flow noise are the principal clinical side effects of COVID-19. Many vaccines were designed to activate the antiviral agent in the United States, United Kingdom, China, etc[7,8].

Many studies have been examinations and predetermined for the advancement of helpful operators for COVID-19 diseases. The researchers were working on the planning of useful antiviral agents and found the design of a new drug [9-11].

At this yet no truly treatment or drugs vaccine was dependent on it[12], but using docking computational chemistry played an essential part in discovering a novel pharmaceutical drugs design[13,14]. The vaccine sometimes takes a time to be tried and is guaranteed to be safe and used for humans[15,16].

There are numerous compounds utilized to treat some illnesses discovered from the plant. Antifungal, antiviral and antibacterial have been characterized as bioactive compounds[17.18].

Docking theoretical studies were applied widely for the characterization of the COVID-19 disease. These computational methods were used to predict the best drug by docking interaction with protein and determining the physical properties[19]. This leads to finding and choosing the preferable drugs for treating the disease[20,21]. The significance of drug design is important to the rise of the COVID-19[22].

Density function theory (DFT) at basis set (B3LYP/6-31G*) method was used for the identification of the physical properties of chloroquine substituents as the treatment of this pandemic[23]. While another treatment of COVID-19 was an investigation by theoretical docking study of chloroquine with coumarin derivatives[24].

Computational chemistry has applied the determination of the physical properties of

Corresponding author e-mail: * ammar74@uomosul.edu.iq , ORCID ID: 0000-0002-7085-4074
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heterocyclic compounds used as antiviral for the treatment of the COVID-19 pandemic[25,26].

Binding values for complex docking between many drugs with ligands (6LU7)[27,28] and (6vxx)[29] have been evaluated.

2. Computational Methods:

All the structures of the proteins of SAR-Cov-2 have been taken and downloaded from the protein data bank website (PDB). The COVID-19 proteins code are (6wtt and 6xa4)[30]. These proteins were removed from their attachments to other molecules like H_2O, alternative molecules, chlorine, and small proteins having a little number of amino acids. Later, these proteins were re-correct the hydrogen atoms in the structure and re-arrangement automatically.

The pharmaceutical compounds were drawn using the Chem-Bio Office 3D version (17.1). All the ligands and the receptor were characterized by their docking by (MOE) software version (2015). The simulation of docking between the proteins and pharmaceutical was done by choosing the active site of the proteins to reach the final configuration which has more stable and less steric energy.

The computational docking for ligand and receptor was determined using a personal laptop having the properties (Intel Core i7-4810) with RAM (8.0 GB) and the operating system is Microsoft Windows 10 Pro at system type (64-bit).

3. Results and Discussion:

The docking study was applied to estimate the docking interaction of several medicines which are showed their formula in fig (1) with different proteins. These medicines were selected because different studies used these in different applications. These proteins were selected depending on their activity in the SAR-Cov2 virus.

3.1 Docking of (twtt):

This protein has in its structure (2326) atoms and (302) residues. So, the total formula contains 1470 carbon atoms, 397 nitrogen atoms, 437 oxygen atoms, and 22 sulfur atoms as shown in fig(2). From this, we can note that there are many active functional groups in these proteins, especially the nitrogen, oxygen, and sulfur atoms. These groups are founded clearly in the proteins as amino-acid like (His), (Phe), and (Glu.).

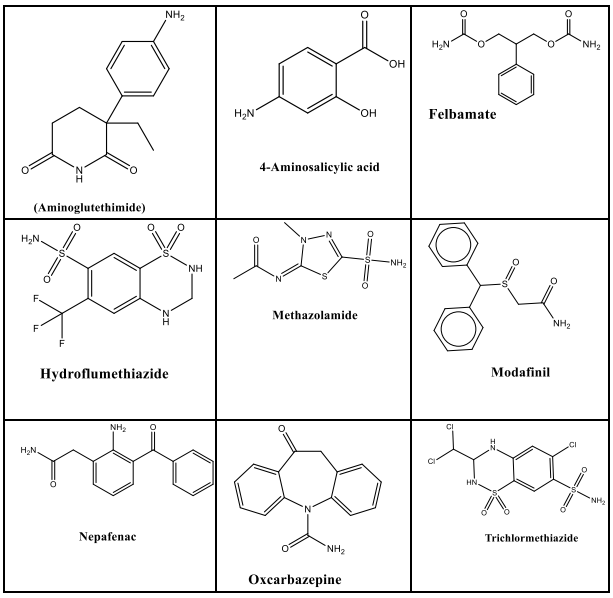


Fig. 1. Molecular structure of pharmaceutical compounds

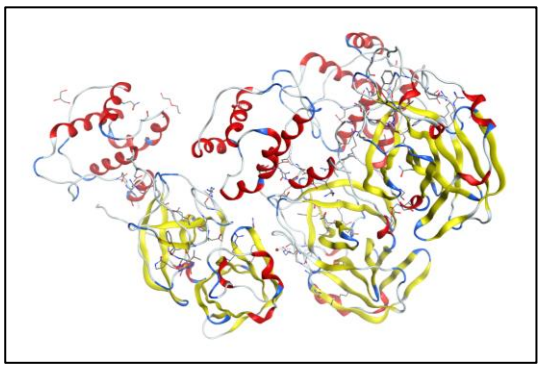


Fig. 2. The structural formula of (6wtt) protein

3.1.1 Docking with Medicines

The results for (6wtt) protein with the binding score energy as (score value) were determined. Where (score value) means the Interactions of inhibitors with the receptor. Selected the best site of the protein to interact with different medicines to characterize the best docking as shown in table (1). The values observed that (A-9, A-4, A-7, A-6, A-3, A-1, A-8, A-5 and A-2) having energy score values (-6.1526, -6.0110, -5.8525, -5.7855, -5.7673, -5.5064, -5.4542, -5.3520 and -4.5548) respectively. This is evidence that all medicines have a higher score value compared to the (A-2) compound.

Table (1) was shown the medicine (Trichlor-methiazide) was having a more stable value (-6.1526), while the medicine (4-Aminosalicylic acid) was less stable with a value (-4.5548) compare to others.

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

Comp. No.	**Medicines**	**Score values**
A-1	(Aminoglutethimide)	-5.5064
A-2	4-Aminosalicylic acid	-4.5548
A-3	Felbamate	-5.7673
A-4	Hydroflumethiazide	-6.0110
A-5	Methazolamide	-5.3520
A-6	Modafinil	-5.7855
A-7	Nepafenac	-5.8525
A-8	Oxcarbazepine	-5.4542
A-9	Trichlormethiazide	-6.1526

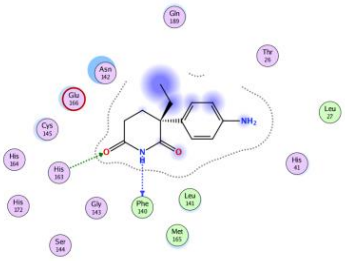
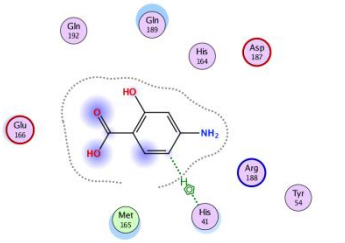
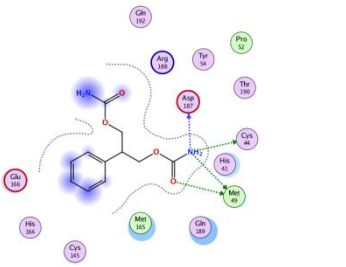
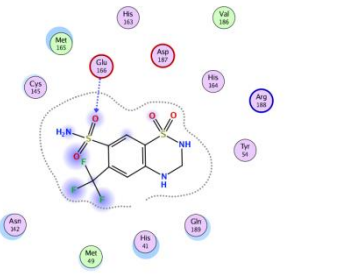
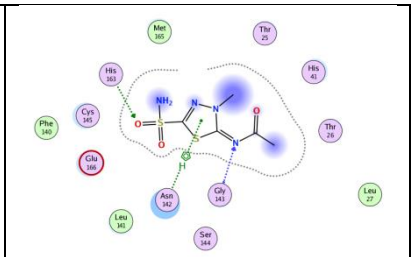
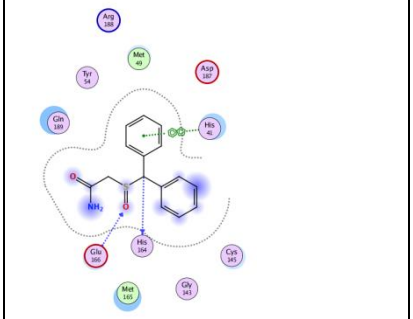
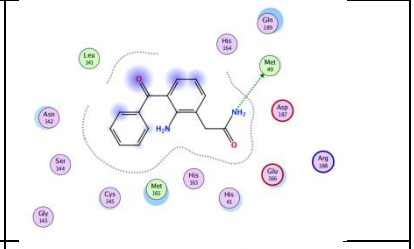
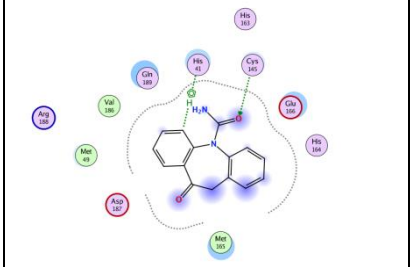
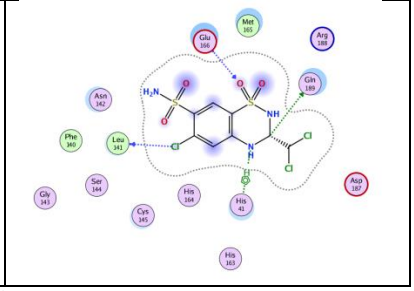
Comp. No.	Docking Interaction
A-1	
A-2	
A-3	
A-4	
A-5	
A-6	
A-7	
A-8	
A-9	

Fig. 3. Docking of the medicines with (6wtt) protein

So, the medicine (Trichlormethiazide) was surrounded by different amino acid groups in protein. The active polar site was contacted between the medicine with the protein by (Glu 166), (Gln 189) by intermolecular hydrogen bond, (Leu 141) by free electrons in chlorine, and (His 41) which was attached by (π) aromatic system as shown in figure (3).

While the medicine (4-Aminosalicylic acid) was in contact with the amino acid group (His 41) by (π) aromatic system.

If we compare the medicine (Trichlormethiazide) with others, we can note that this compound was having three chlorine atoms in the formula of the structure. This indicates the compound was more polar and active compared to other compounds which also have active groups like (NH2, =O). For these reasons, the medicine title (Trichlormethiazide) was more stable compared to the others[32].

3.2 Docking of (6xa4):

This protein contains (2356) atoms and about (304) residues. The total formula included (1494) carbon atoms, (398) nitrogen atoms, (442) oxygen atoms, and (22) sulfur atoms as shown in fig(4).

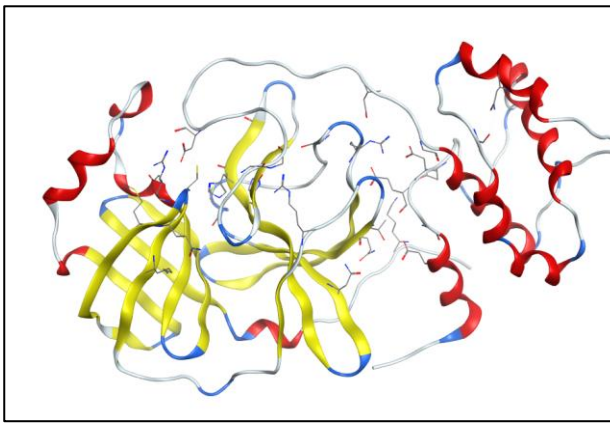


Fig. 4. The structural formula of (6xa4) protein

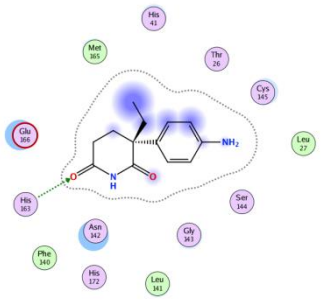
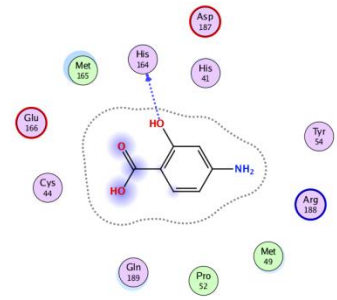
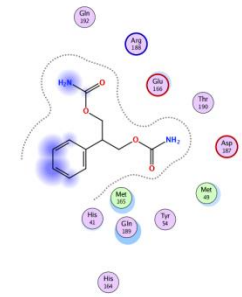
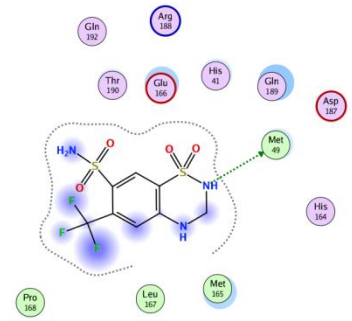
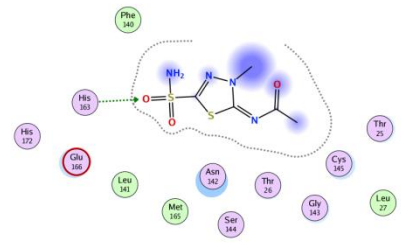
3.2.1 Docking with Medicines

Later, we selected the best site of the protein to interact with different medicines to characterize the best docking as shown in the following table.

Table 2. Score values for docking of (6xa4) protein with medicines

Comp. No.	Medicines	Score values
A-1	(Aminoglutethimide)	-5.2290
A-2	4-Aminosalicylic acid	-4.5038
A-3	Felbamate	-5.6214
A-4	Hydroflumethiazide	-5.2556
A-5	Methazolamide	-5.7868
A-6	Modafinil	-5.8001
A-7	Nepafenac	-5.2956
A-8	Oxcarbazepine	-5.2956
A-9	Trichlormethiazide	-6.5936

The medicine (Trichlormethiazide) has to have a more stable value (-6.5936), while the medicine (4-Aminosalicylic acid) was less stable with a value (-4.5038) compare to others as shown in table (2).

Comp No.	Docking Interaction
A-1	
A-2	
A-3	
A-4	
A-5	

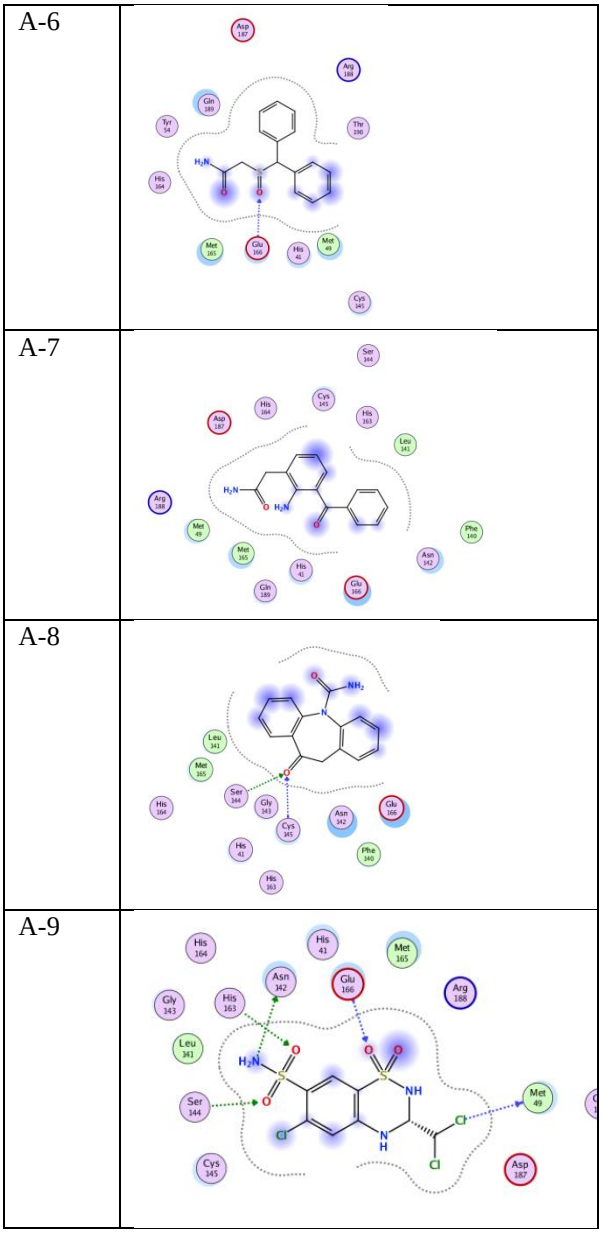


Fig. 5. Docking of the medicines with (6xa4) protein

Trichlormethiazide medicine was besetment by many amino acid compounds. The active site was near the protein by (His 163), (Asn 142), (Glu 166), (Met 49), and (Ser 144) by intermolecular hydrogen bond by free electrons in chlorine, (-NH2) and ketone. While (4-Aminosalicylic acid) medicine was attached with (His 146) by a hydrogen atom.

So, the medicine (Trichlormethiazide) contained three chlorine atoms in the formula of the structure which makes it more polar and active compared to other compounds besides having active groups like (NH2, =O) in his formula structure. For these reasons, the medicine title (Trichlormethiazide) was more stable compared to the others.

Figure (6) was viewed the comparison between two medicines (Trichlormethiazide) and (4-Aminosalicylic acid) with two proteins. From this figure, we can conclude that (Trichlormethiazide) was more active in binding docking and more stable with (6xa4) compare with (6wtt). While medicine (4-Aminosalicylic acid) was less stable compared to others.

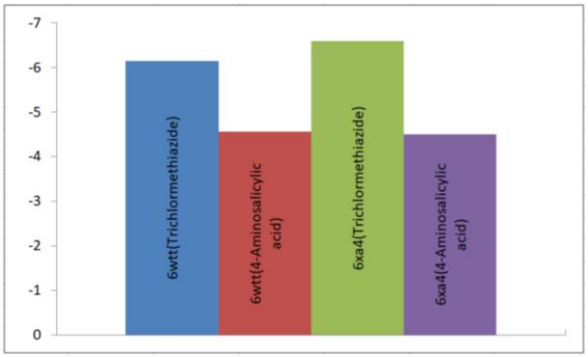


Fig. 6. Comparison score between medicines with proteins

4. Conclusion:

The score values give to us good information about the interaction between the drug and the acceptor[31]. The docking results showed that medicine (Trichlormethiazide) was the most active compared with others against the proteins (6wtt) and (6xa4) with values (-6.1526) and (-6.5936) respectively. While medicine (4-Aminosalicylic acid) was having less docking binding with the previous proteins with values (-4.5548) and (-4.5038) respectively.

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