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A Molecular Docking Approach to Evaluate the Pharmacological Properties of 1-(4-amino-1,2,5-oxadiazol-3-yl)-N'-(1-(3-hydroxyphenyl)vinyl)-5-(thiophen-2-yl)1H-1,2,3-triazole-4-carbohydrazide Treatment Candidate for Use against COVID-19

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Abstract: Abstract: In recent years, the new Coronavirus known as COVID-19 has caused a pandemic that has caused severe health problems. The virus is spreading rapidly worldwide, and finding potential antiviral drugs that can inhibit virus proteins is crucial. Recently, CoVID-19 crystal structure elucidated such as major protease Mpro (PDB: 6LU7), SARS-CoV- main peptidase (2GTB), human ACE2 (PDB: 1O86), human coronavirus papain-like proteases (PDB: 4OW0) SARS-Coronavirus NSP12 protein (PDB: 6NUR), COVID-19 main protease (PDB:6lu7). These proteins are essential for virus replication, so they are potential targets for CoVID-19 drugs. In this study, we used the molecular docking models to study the binding interactions between anodyne called 1-(4-amino-1,2,5-oxadiazol-3-yl)-N'-(1-(3-hydroxyphenyl)vinyl)-5-(thiophen-2-yl)-1H-1,2,3-triazole-4-carbohydrazide(Zinc ID 000002613203) using MOE 2015.10. It has been observed Obtained results by molecular docking showed that a stronger bond and high affinity with 4OW0 -8.1949, 6lu7 -7.7925, 1O86-7.5757, -6.7832 -7.4101, 2GTB -7.2510 kcal/mol). Based on the binding energy score, this compound are suitable for testing against Coronavirus and could be considered potential inhibitor of COVID-19 infection.)

Keywords: Anti-viral effects; Molecular docking; MOE; COVID-19

1 Introduction

The recent outbreak of the deadly coronavirus pandemic (COVID -19) has raised severe global health concerns. Viruses are spreading rapidly in the current situation.

Since its emergence in late December 2019 in China, the number of confirmed cases is 464,809,377, including 6,062,536 deaths worldwide, and the number of infections continues to increase (WHO Coronavirus (COVID-19) Dashboard, 2022). Due to The absence of approved medications, new therapeutic molecules must be discovered (Gurung et al. 2021).

Drug development of a new drug usually takes more than ten years (Songet al. 2009). Even with the high investment and time required to discover new medicines, less than 14% of clinical trials are successful (Zhong et al. 2018,Gurung et al. 2021). The cost of bringing a medication to market can be up to 2 billion USD(DiMasiet al. 2016).

Computer simulations have aided in accelerating the discovery and development of new medications and drugs by reducing costs and time (Gurung et al., 2021). Molecular docking is commonly employed to study silico binding between proteins and ligands to prioritize compounds and identify new lead medication compounds. This could be a helpful tool for developing and discovering new potential antiviral inhibitors against SARS-CoV-2 (Serafim et al. 2021).

Nowadays, molecular docking programs are widely and routinely used in computational drug discovery, mainly in virtual library screening campaigns (VS). (Jorgensen 2004). The first step of structure-based drug discovery (SBDD) is to identify the drug ligand that best fits the binding pocket of the target protein. This method was developed to predict the geometry of binding complexes between proteins and ligands (Kuntz et al. 1982,Gioia et al. 2017).

Our study aims to find an effective drug candidate (Anodyne Zinc ID 2613203) against COVID -19, targeting the proteins 2GTB and 6LU7 and 1O86 and 6NUR, and 4OW0 and the major protease of COVID -19 by using A Computer simulations methods.

2 Materials and Method

All docking experiments were used MOE 2015.10 for the analysis. The simulation was performed on a high-performance computer .

2.1. Preparation of Ligand

Ligand structures were retrieved from the Zinc database (http://zinc.docking.org). Smiles were used to load the structures into MOE and with the partial charges added. For docking purposes, structures were reduced and stored as a database. (Adebambo 2020).

2.2. Preparation of Proteins

Crystal structure of 2GTB and 6LU7 and 1O86 and 6NUR and 4OW0 proteins was retrieved from the Protein Data Bank (http://www.rcsb.org) with 2.16 Å, 2.00 Å, 2.16 Å, 2.00 Å, 2.10 Å, 3.10 resolution respectively.

The structure of the protein was refined by removing ligands and water molecules already bound to it. and protein preparation by, 3D protonation was performed in MOE. to remove defects after correcting, The binding site of the protein was found using MOE software's site finder.

2.3. Molecular docking

Using MOE docking tool, was accomplished to docking the substance anodyne (Zinc ID 2613203) to the allosteric ligand binding site of 2GTB and 6LU7 and 1O86 and 6NUR and 4OW0 proteins. The potential binding pocket was identified using the Site Finder Tool from MOE and then subjected to a docking process. Using a London dG scoring function, the top five docked poses were identified. The docking process was refined by applying a force field algorithm that kept the receptor rigid. Based on the root mean square deviation (RMSD), measured in angstroms (Å), and the docking score, the best interacting ligands and molecules were selected.

Previously reported co-crystallized ligand. Ligand-receptor binding analysis was performed using the LigX tool in MOE. The system visualizes potential residues interacting with ligand molecules using 2D images representing the forces stabilizing the ligand molecules in the binding pockets of the receptor (Khan et al. 2017).

3 Results

In the present study, virtual screening of the (Anodyne Zinc ID 2613203) substance (Figure 1) against 2GTB and 6LU7 and 1O86 and 40W0 6NUR .Where these proteins have been presented as attractive drug targets.(Pires et al., 2015,Dainaet al. 2017)

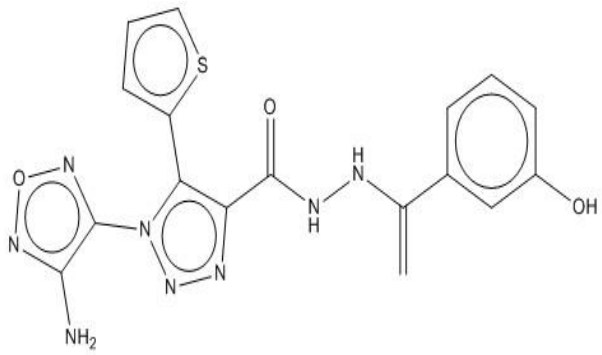

Fig. 1 Structure of Anodyne Zinc ID 2613203 substance

Docking studies were performed using the Molecular Operating Environment (MOE 2015.10). The results of these experiments showed strong interactions of the potential compound candidates anodyne Zinc ID 2613203 substance against the COVID -19 major protease (PDB:6lu7) and SARS-CoV major peptidase (PDB: 2GTB) and 1O86 and 40W0, 6NUR. After the successful docking of these compounds to the COVID -19 target proteins mentioned above, different modes of ligand-protein interactions with a specific docking score (binding energy) are generated. Binding modes with the lowest binding energies are considered the best binding modes since they are the most stable for the ligand. The observed binding energy results are summarized in Table 1,2,3,4,5.

Based on the molecular docking result, Anodyne Zinc ID 2613203 substances could be useful in treating infected patients. We find that the docking score reaches -8.1949 in 40W0, -7.2510 in 2GTB, -7.5757 in 1O86, -6.7832 in 6NUR, and -7.7925 in 6lu7.

The interaction of specific amino acids involved in ligand-protein interactions was also recorded. Followingthemolecular docking results, the 2-dimensional visualization results of the ligand-residue interactions showed that the (Anodyne Zinc ID 2613203) substance

latches into the binding pocket in 1086 with four interactions; it has a hydrogen bonding interaction with Met223 in the binding site and three pi-Hydrogen interactions with different amino acids contained within the binding pocket, these a six-ring Ile204 pi-Hydrogen, a five-ring Lys118 pi-Hydrogen, and a five-ring Glu403 pi-H interaction. (Figure 2).

While the anodyne Zinc ID 2613203 substance compound is bound to the 2GTB protein, it has a total of four binding interactions with the amino acids in the binding pocket, showing that the drug molecule latches onto the binding pocket with four interactions, it has hydrogen bonding interactions with His in the binding site. And two pi-Hydrogen interactions with different amino acids within the binding pocket, these one five-ring Asn142 pi-Hydrogen, and one five-ring Glu166 pi-Hydrogen interaction (Figure 3).

The ligand interaction with the 4OW0 protein (Figure 4) showed that the Anodyne Zinc ID 2613203 latches into the binding pocket with four interactions. With the amino acids

in the binding pocket, it has one hydrogen bonding interaction with Asp165(A) in the binding site and three pi-Hydrogen interactions with different amino acids within the binding pocket, these one 5 ring Tyr(A) 269 and Gly(A)164 and Asp165(A) pi-Hydrogeninteraction.

As shown in Figure 5 below, the ligand occupied the binding pocket of the 6NUR protein, and the Anodyne had four hydrogen bonds with amino acids Ala-554 and Thr-556 present in the binding pocket, and two pi-Hydrogen interactions with different amino acids within the binding pocket, namely a 6-ring Arg624 pi-Hydrogen and a 5-ring Arg553 pi-Hydrogen interaction.

The ligand interaction with 6LU7 protein (Figure 6) showed that the Anodyne Zinc ID 2613203 latches into the binding pocket with six interactions, the amino acids in the binding pocket interacting strongly with two Glu, two His, and one Cys amino acids. And two pi-Hydrogen interactions with different amino acids within the binding pocket, these Two 5-ring Gln(A) 189 and Gln189(B) pi-Hydrogen interactions.

Table 1. Interaction between drug candidate and 2GTB and their docking properties of the top five poses

no.	S	rmsd_ refine	E_conf	E_place	E_score1	E_refine
1	-7.2510	1.6070	88.2360	-89.8618	-12.3420	-38.9720
2	-7.0690	1.6012	82.5988	-56.8477	-10.2660	-40.0395
3	-6.8280	1.5127	74.0142	-83.6527	-9.9414	-42.3033
4	-6.7807	2.2541	79.3597	-92.3093	-10.8162	-40.2780
5	-6.7548	1.4512	73.7242	-106.0715	-11.2040	-41.5857

Table. 2. Interaction between drug candidate and 1086 and their docking properties of the top five poses .

no.	S	rmsd_ refine	E_conf	E_place	E_score1	E_refine
1	-7.5757	1.0870	76.0101	-87.7858	-10.7714	-44.6827
2	-7.2876	1.8361	80.5905	-105.1578	-10.2660	-40.7860
3	-7.1614	1.3610	79.0984	-101.0885	-10.3269	-38.9334
4	-7.0618	2.1344	82.5177	-65.1269	-9.9578	-41.7902
5	-7.0274	1.4959	84.4009	-90.1260	-11.3677	-39.2677

Table. 3. Interaction between drug candidate and 40W0 and their docking properties of the top five poses .

no.	S	rmsd_ refine	E_conf	E_place	E_score1	E_refine
1	-8.1949	1.7178	80.0550	-104.5792	-11.1493	-48.3560
2	-8.1541	1.2627	74.4491	-81.7984	-11.4903	-48.0648
3	-8.0749	2.2633	76.6276	-89.0673	-11.6562	-46.2307
4	-7.6948	1.7017	74.5244	-73.9517	-11.5709	-44.6842
5	-7.6351	1.4096	76.8360	-109.5280	-11.2194	-43.7298

Table. 4. Interaction between drug candidate and 6NUR and their docking properties of the top five poses .

no.	S	rmsd_ refine	E_conf	E_place	E_score1	E_refine
1	-7.4101	2.2200	79.3847	-70.9006	-10.4089	-45.2058
2	-6.8108	3.5918	79.8446	-70.7154	-10.5112	-34.4157
3	-6.7832	1.0721	75.0903	-80.0705	-10.1899	-35.9292
4	-6.5244	1.4898	76.9420	-97.5033	-11.6161	-36.2727
5	-6.5037	1.5257	75.0589	-76.7025	-10.2171	-32.9803

Table. 5. Interaction between drug candidate and 6lU7 and their docking properties of the top five poses .

no.	S	rmsd_ refine	E_conf	E_place	E_score1	E_refine
1	-7.7925	1.5134	80.3739	-80.8232	-11.9235	-45.9976
2	-7.3862	1.5224	80.0461	-77.8064	-10.7242	-39.1877
3	-6.9489	1.1649	84.8352	-99.1665	-11.5751	-40.1935
4	-6.8982	2.4029	81.2241	-101.2040	-10.9526	-40.3345
5	-6.8760	1.7116	75.2210	-89.9736	-12.2249	-42.6265

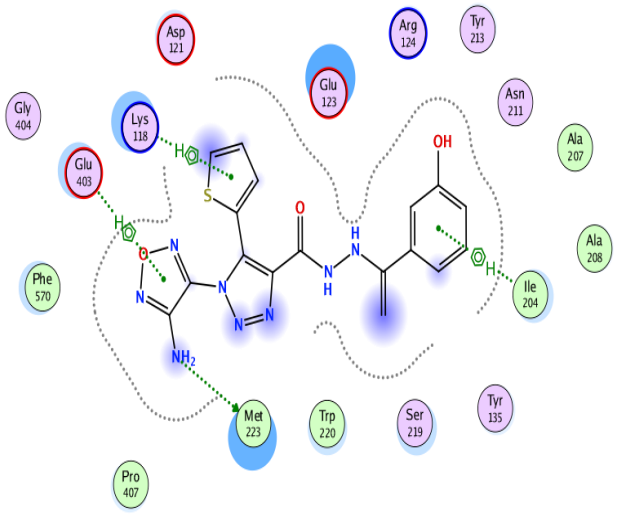

Figure 2 The interaction of Anodyne Zinc ID 2613203 substance with the amino acids in the binding pocket of 1086

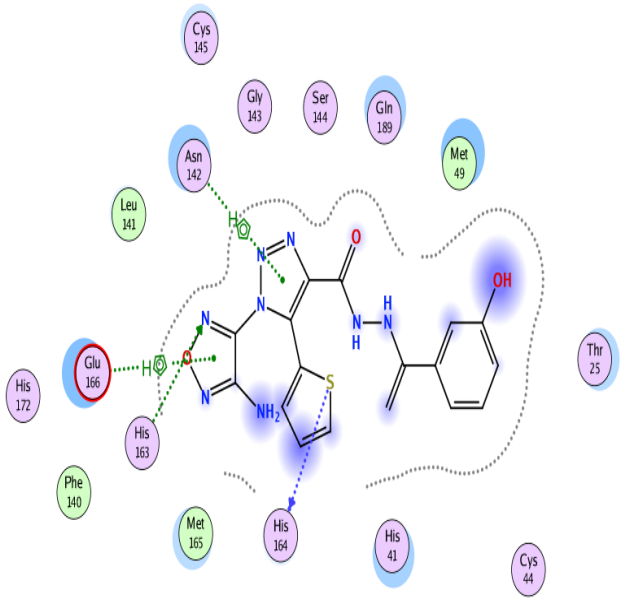

Figure 3. The interaction of Anodyne Zinc ID 2613203 substance with the amino acids in the binding pocket of 2GTB

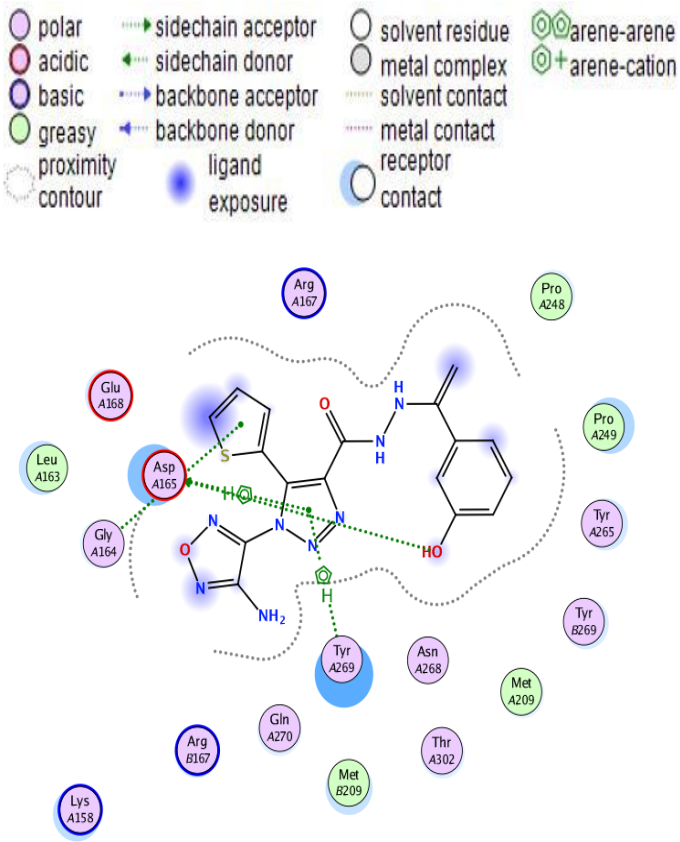

Figure 4. The interaction of Anodyne Zinc ID 2613203 substance with the amino acids in the binding pocket of 40W0

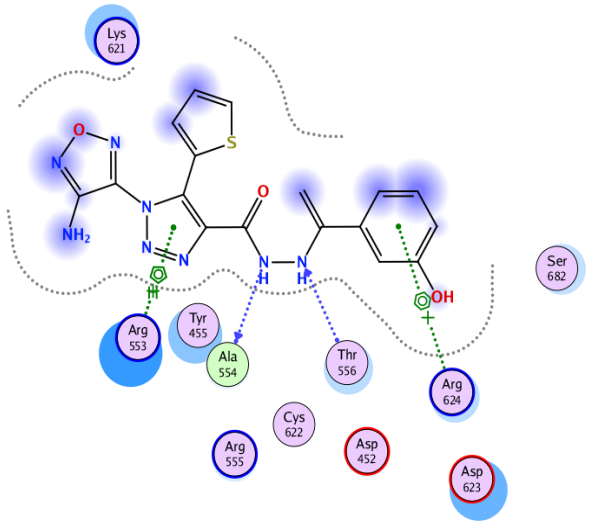

Figure 5. The interaction of Anodyne Zinc ID 2613203 substance with the amino acids in the binding pocket of 6NUR

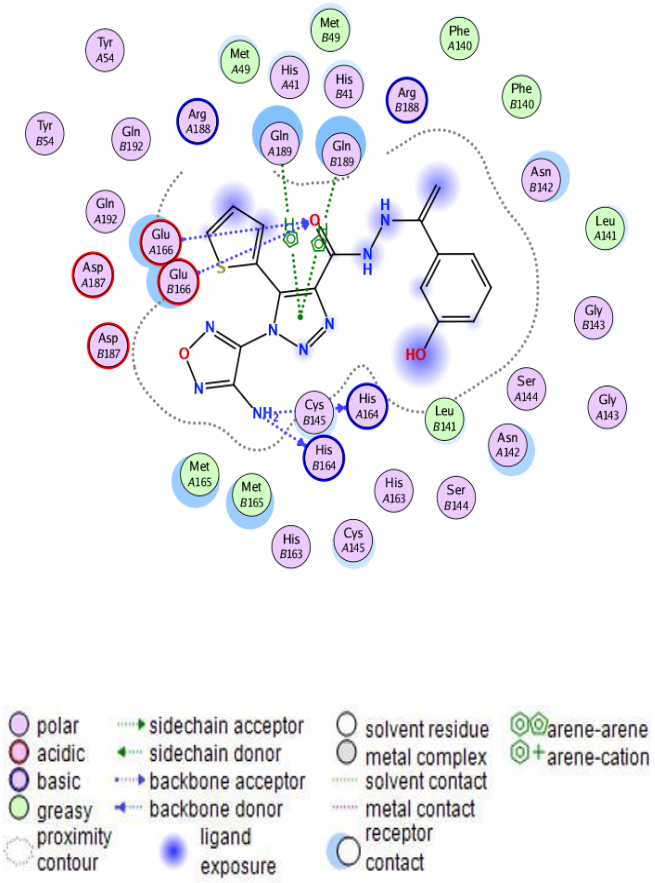

Figure 6. The interaction of Anodyne Zinc ID 2613203 substance with the amino acids in the binding pocket of 6Lu7.

4 Discussion

This study involves the In silico interactions of anodyne Zinc ID 2613203 substances. With int he proteins 4OW0, 6lu7, and 6NUR, 1O86, 2GTB, and 6NUR which play a role in virus entry into host cells and virus replication.

Based on the docking results, the ligands found potential inhibitory effects of 4OW0, 6lu7, and 6NUR, 1O86, 2GTB, 6NUR protein with binding energy (-8.1949, -7.7925, -7.5757, -7.4101, -7.2510 kcal/mol) when comparing the efficacy of anodyne Zinc ID 2613203 substances.

Comparison with other drugs used to treat covid-19 shows the compound chloroquine (-6.30 kcal/mol) and hydroxychloroquine (-7.28 kcal/mol) mentioned in the study.(Amin and Abbas 2020) atazanavir (-7.912) , Remdesvir (-7.804) , Amprenavir (-7.747) , Lopinavir -(7.041) , Nelfinavir (-6.73) , Oseltamivir (-5.825) , Tipranavir -(5.64) , Galidesvir (-4.967) kcal/mol (Kumar et al., 2020). The proposed compound has high docking scores.

The compound contains a sulphur atom in its composition. Sulphur is considered to be nucleophilic because its size makes it easy to polarize. S-atoms in compounds show H-bonding interactions with the catalytic residue His164 of 2GTB. In general, the Nitrogen groups in the aliphatic and cyclic structures of the substance form strong and dense H-bonds with the critical catalytic residues of 40W0, 6LU7, protein. In addition, there are hydrogen bonds and pi-Hydrogen interactions with various amino acids within the binding pocket in 1O86, 2GTB), 4OW0), 6NUR, and 6LU7. All these molecular interaction properties enhance the inhibition potential of anodyne Zinc ID 2613203 substance for CoVID-19.

5 Conclusion

Corona disease is still a major problem that should be solved by developing new bioactive agents. The appearance of new mutations leads to problems with drug resistance. This study addresses the in silico interactions of 1-(4-amino-1,2,5-oxadiazol-3-yl)-N'-(1-(3-hydroxyphenyl)vinyl)-5-(thiophen-2-yl)-1H-1,2,3-triazole-4-carbohydrazide with protein 4OW0, 6lu7, and 6NUR, 1O86, 2GTB, 6NUR, which plays a role in the method of virus entry into host cells and virus replication. Based on the docking results, the ligands found potential inhibitory effects of 4OW0, 6lu7, and 6NUR, 1O86, 2GTB, 6NUR protein with binding energy (-8.1949, -7.7925, -7.5757, -7.4101, -7.2510 kcal/mol). Suggesting that it is a potent candidate for further in vitro and in vivo studies as an experimental drug for use against Covid-19.

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Conflict of interest:

The author declares that there are no conflicts of interest related to the publication of this article

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