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Dapsone with Amino Acids and Docking with Multiple Proteins as A Covid-19 Treatment: A Theoretical Study

Aswan Najah Al-Deen Abed[a], Omar Mohammed Yahya[b], Ammar Abdulsattar Ibrahim[c, 1]

[a]College of Law, University of Ninevah, Mosul, Iraq
[b]Department of Biochemistry, College of Medicine, University of Mosul, Mosul, Iraq
[c]Department of Chemistry, College of Science, University of Mosul, Iraq

Abstract: The deadly illness COVID-19 claims a significant number of lives every day. The dapsone molecule has been proposed as a potential antiviral for the treatment of COVID-19 illnesses based on molecular docking simulations in this study. Additionally, look into how mono- and di-amino acid molecules react with dapsone. To investigate molecule geometries, electronic properties, and molecular electrostatic potential, Hartree Fock at the (STO-3G) technique was used. To evaluate dapsone's pharmacological effects against coronavirus infections, docking calculations were made. This study is a component of our efforts to find a potent antiviral agent to treat this deadly disease, which unquestionably dictates medicinal chemistry efforts.

Keywords: Docking, COVID-19 proteins, Theoretical Chemistry, Dapsone, MOE.

1. Introduction

The coronavirus was discovered in people for the first time in late December 2019 in Wuhan, China, and it spread like a pandemic very swiftly. Around 40 million people had the infection as of November 1, 2020, and more than a million had died. It's important to note that this pandemic's symptoms are comparable to those of the flu. Fever, exhaustion, runny nose, dry cough, and headache are the primary clinical symptoms of COVID-19 [1,2].

Dapsone is a sulfone-containing compound with antibiotic anti-inflammatory and antibacterial effects. The main medicine in a multidrug leprosy treatment regimen suggested by the World Health Organization is dapsone. Dapsone is swiftly and almost fully absorbed from the gastrointestinal system. A bigger, blinded randomized study should be conducted as soon as possible to see if dapsone improves COVID-19 results. Earlier observations hinted at a potential survival advantage from including dapsone in the standard of treatment for COVID-19 patients hospitalized [3-5]. Using the azo-coupling procedure, dapsone was chemically coupled with five different phytochemicals, resulting in dapsone-phytochemical conjugates. Before chemical synthesis and spectrum characterizations, the biological activities were confirmed using a computational chemistry and quantum mechanics tool [6]. Currently, COVID-19 cannot be treated or prevented with a specific drug or immunization. There is currently no specific drug or immunization that may be used to prevent or treat COVID-19. As a result, there has been an increase in demand for COVID-19-related medicines, vaccines, tests, and reagents. Due to this circumstance, dishonest people may be able to sell fraudulent medical supplies [7,8].

Because there are no effective authorized treatments or medications, the computational technique offers a viable option for pharmaceutical companies to develop novel pharmaceuticals [9,10]. Calculations using DFT and molecular docking of chloroquine by evaluated the (HOMO, LUMO) energy gap [11] derivatives are one of the medications that have been investigated against the coronavirus pandemic and have shown to be effective at the B3LYP/6-31G* method [12].

[1] Corresponding Authors
e-mail: ammar74@uomosul.edu.iq

To evaluate the effectiveness of pharmaceuticals as antivirals against COVID-19, molecular docking simulations were employed. By simulating the geometrical characteristics of these molecules and their interactions, pharmaceutical compounds are produced using a computer-aided process called docking [13,14]. For many pharmacological molecules, the theoretical calculations using Gaussian 03w were performed. Computed variables such as HOMO, LUMO, total energy, Gibbs Free Energy, etc. were crucial in predicting the realistic lipophilicity values [15]. The calculated parameters were entered into a model to anticipate the practical outcomes (Log P) depending on the (HOMO, LUMO) parameters [16].

Simulations of molecular dynamics were run on drug-protein complexes to gain a better understanding of the ligand-COVID-19 affinity and to assess the ligands' stability inside the protein's binding region [17]. SARS-CoV-2's molecular docking technique was used to analyze bioactive chemicals discovered in plants. The docking score was determined by selecting the optimal shape of the protein-ligand complex [18].

Natural compounds with antiviral activity can be employed as a starting point for identifying prospective bioactive chemical candidates to combat SARS-CoV-2. Numerous plant bioactive substances have been found to have antiviral, antifungal, and antibacterial activities [19,20]. The physical characteristics of these medicines' compounds and their complexation with alanine were studied using a computational investigation of the interaction of ten pharmaceuticals [21].

Thermodynamic parameters for the complexation's electrochemical properties were examined using the voltammetric method [cadmi-um (II)-tyrosine] [22] and [paracetamol-alanine] [23] compounds. Different approaches to theoretical calculations have been used to examine the electrical characteristics of antipyrine theoretically. Because of their biological and medicinal significance, these metabolites are of great interest [24].

Theoretically, it was possible to identify pharmacological compounds that had an amino group in their structure. Several types of computations were used to conceptually evaluate the drugs. Linearity was shown by the correlation between experimental results and evaluated physical characteristics. Docking was utilized to analyze drug-protein interactions. Every drug was paired with a protein to give the docking combinations the best energy stability [25].

Finally, docking calculations were performed using four structures of COVID-19 (PDB codes: 6WTT, XA4, 6XBG, 6XFN, and 7JRN) (http://www.rcsb.org/). Based on the binding affinities and the different interactions that exist between amino acid residues and ligands, molecular docking results were discussed.

2. Computational Method

The basic structures of the dapsone and amino acid molecules were modeled using the GaussView tool[26]. Then, using the Gaussian 05 software, the molecule geometries in the gas phase were optimized using the Hartree Fock (HF) technique at basis set (STO-3G). The compounds' lowest energy conformations were gathered and used as computing input data. Using software for the molecular operating environment (MOE) [27], drug coordinates were chosen for each component. The polar hydrogen atoms are combined by adding the atoms to the protein and ligand structures.

3. Results and discussion

Drugs can be linked to amino acids. The aim of the docking, the type of functional groups available on the parent drug, the chemical mechanisms of the docking, and the safety of the pro-moiety all play a role in this relationship. Amino acids are protein building blocks that are usually viewed as harmless. While docking with medicines, the majority of amino acids generate amides. In medicines, α-amine or -carboxylic group is connected to functional groups such as (-=CO, -OH, -NH2). A variety of amino acids have been created to aid sufferers. A sulfone that is effective against a variety of bacteria. Its method of action is likely to be similar to that of sulfonamides, which block folic acid production in vulnerable species. The differences in energies (ΔE) between LUMO and HOMO were used to assess the stability as shown in Figure. 1-4 and Table 1.

So, Fig 5. and 6. show the suggested structure of interaction between the dapsone with amino acid. The binding was selected between the amnio atom of dapsone and with hydroxyl atom in amino acid.

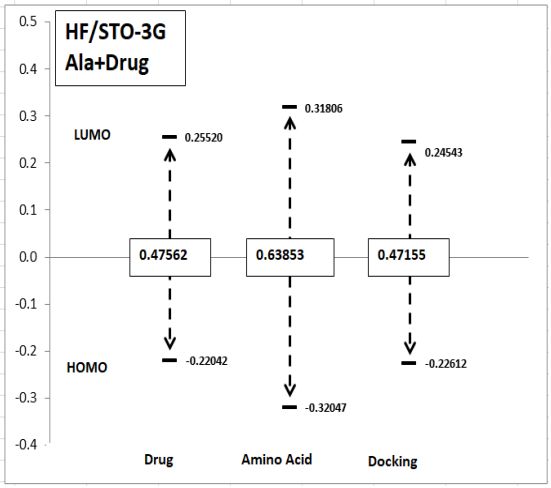

Figure. 1. Energy gap for alanine with drug

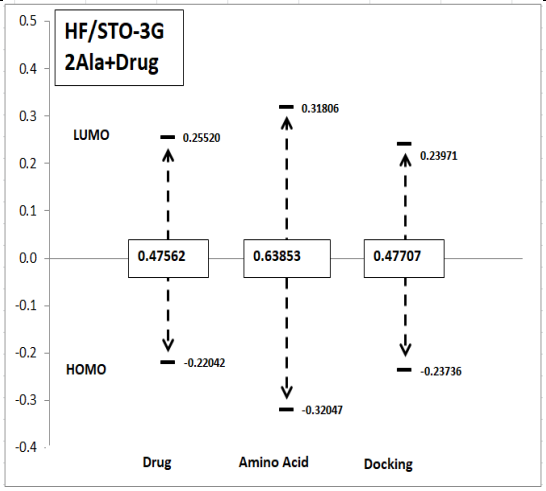

Figure. 2. Energy gap for two alanine with drug

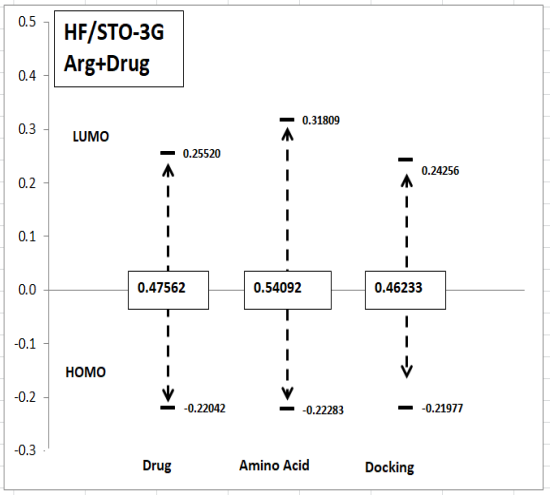

Figure 3 Energy gap for arginine with drug

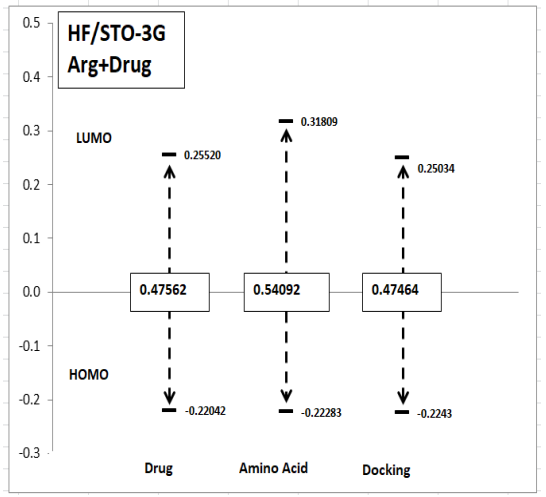

Figure.4 Energy gap for two arginine with drug

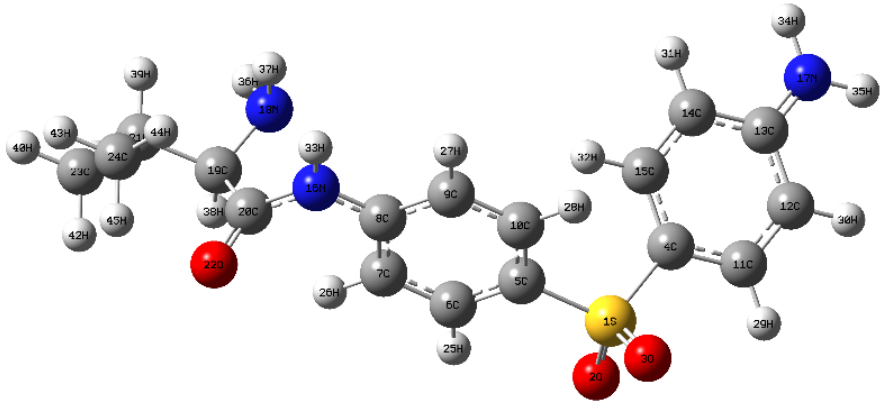

Figure 5. Docking structure of Valine with dapsone

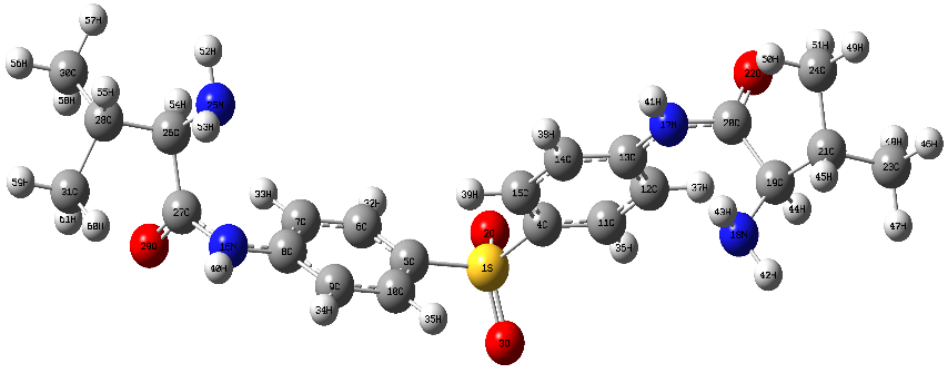

Figure 6. Docking structure of two compounds of Valine with dapsone

Table 1. The differences in energies (LUMO-HOMO) for drugs, amino acids, and docking

Amino Acid	HOMO (a.u)	LUMO (a.u)	Δ Drug	Δ Amino acid	Δ Docking
Dapsone	-0.2204	0.2552	0.4756		
Ala	-0.3205	0.3181		0.6385	0.4716
Arg	-0.2228	0.3181		0.5409	0.4623
Asn	-0.3097	0.3191		0.6288	0.4671
Asp	-0.3233	0.3032		0.6265	0.4618
Cys	-0.2680	0.3140		0.5819	0.4744
Gln	-0.3028	0.3189		0.6216	0.4769
Glu	-0.3204	0.3124		0.6328	0.4693
Gly	-0.3275	0.3169		0.6444	0.4745
His	-0.2590	0.3023		0.5613	0.4769
Ilu	-0.3122	0.3105		0.6227	0.4733
Lus	-0.3118	0.3204		0.6322	0.4774
Lys	-0.3112	0.3202		0.6314	0.4696
Meth	-0.2491	0.3175		0.5666	0.4692
Phe	-0.2725	0.2638		0.5363	0.4671
Pro	-0.3059	0.3170		0.6229	0.4637
Ser	-0.3219	0.3164		0.6383	0.4746
Thr	-0.3190	0.3172		0.6362	0.4744
Trp	-0.2107	0.2400		0.4506	0.4504
Tyr	-0.2407	0.2593		0.5000	0.4747
Val	-0.3128	0.3169		0.6297	0.4747

Table 2. Physical properties of the dapsone, amino acid, and docking between them

Amino Acid	HOMO (a.u)	LUMO (a.u)	ΔH (a.u)	ΔG (a.u)	ΔS Cal/Mol-K	Dipole moment
Dapsone (Dap)	-0.22042	0.25520	0.26873	0.20781	128.20	8.25
H2O	-0.39262	0.58179	0.02816	0.00664	45.28	1.71
Ala	-0.32047	0.31806	0.13330	0.09469	122.35	2.10
Ala + Dap	-0.22612	0.24543	0.37196	0.29554	160.83	6.38
Δ (Prod. – React.)			-0.002	0.000	-44.437	-2.258
2Ala+ Dap	-0.23736	0.23971	0.47519	0.38325	193.49	8.82
Δ (Prod. – React.)			-0.004	-0.001	-88.845	-0.208
Arg	-0.22283	0.31809	0.27241	0.21574	119.27	2.74
Arg+Dap	-0.21977	0.24256	0.51137	0.41818	196.12	5.96
Δ (Prod. – React.)			-0.002	0.001	-6.067	-3.318
2Arg+Dap	-0.22430	0.25034	0.75308	0.62546	268.61	6.88
Δ (Prod. – React.)			-0.004	-0.001	-7.565	-3.428
Asn	-0.30973	0.31905	0.16642	0.11977	98.19	3.62
Asn+Dap	-0.23039	0.23671	0.40534	0.32279	173.74	9.19
Δ (Prod. – React.)			-0.002	0.002	-7.367	-0.968

2Asn+Dap	-0.22461	0.25402	0.54102	0.43315	227.05	5.87
Δ (Prod. – React.)			-0.004	-0.001	-6.965	-6.198
Asp	-0.32332	0.30316	0.15223	0.10585	97.61	2.39
Asp+Dap	-0.22781	0.23403	0.39116	0.30880	173.33	7.81
Δ (Prod. – React.)			-0.002	0.002	-7.197	-1.118
2Asp+Dap	-0.22727	0.25114	0.51261	0.40498	226.53	6.48
Δ (Prod. – React.)			-0.004	-0.001	-6.325	-3.128
Cys	-0.26796	0.31396	0.13473	0.09163	90.72	2.38
Cys+Dap	-0.22217	0.25218	0.37324	0.29228	170.40	5.15
Δ (Prod. – React.)			-0.002	-0.001	-3.237	-3.768
2Cys+Dap	-0.22806	0.25032	0.47778	0.37671	212.74	6.84
Δ (Prod. – React.)			-0.004	-0.001	-6.335	-2.748
Gln	-0.30277	0.31885	0.20173	0.15107	106.62	3.34
Gln+Dap	-0.24467	0.23225	0.44068	0.35361	183.26	6.78
Δ (Prod. – React.)			-0.002	0.001	-6.277	-3.098
2Gln+Dap	-0.22790	0.25108	0.61238	0.49855	239.59	3.23
Δ (Prod. – React.)			-0.003	0.002	-11.285	-8.278
Glu	-0.32038	0.31241	0.18746	0.13693	106.34	1.55
Glu+Dap	-0.22814	0.24114	0.42643	0.33969	182.56	5.35
Δ (Prod. – React.)			-0.002	0.002	-6.697	-2.738
2Glu+Dap	-0.22876	0.24983	0.58317	0.46794	242.54	5.88
Δ (Prod. – React.)			-0.004	0.000	-7.775	-2.048
Gly	-0.32749	0.31692	0.09838	0.06278	74.93	1.84
Gly+Dap	-0.22764	0.24685	0.33698	0.26322	155.25	6.28
Δ (Prod. – React.)			-0.002	-0.001	-2.597	-2.098
2Gly+Dap	-0.23746	0.23921	0.40523	0.31862	182.30	8.39
Δ (Prod. – React.)			-0.004	-0.001	-5.195	-0.118
His	-0.25900	0.30226	0.19582	0.14777	101.13	5.24
His+Dap	-0.21851	0.25834	0.43459	0.34903	180.07	7.32
Δ (Prod. – React.)			-0.002	0.000	-3.977	-4.458
2His+Dap	-0.21884	0.26104	0.60044	0.49047	231.46	8.23
Δ (Prod. – React.)			-0.004	0.000	-8.435	-7.078
Ilu	-0.31217	0.31052	0.23933	0.19200	99.62	1.77
Ilu+Dap	-0.22271	0.25061	0.47823	0.39322	178.93	6.11
Δ (Prod. – React.)			-0.002	0.000	-3.607	-2.198
2Ilu+Dap	-0.22974	0.24833	0.68773	0.57859	229.69	8.10
Δ (Prod. – React.)			-0.003	0.000	-7.185	-0.268
Lus	-0.31184	0.32038	0.23915	0.19075	101.87	2.09
Lus+Dap	-0.22364	0.25371	0.47767	0.39154	181.28	5.43
Δ (Prod. – React.)			-0.002	0.000	-3.507	-3.198
2Lus+Dap	-0.22717	0.25166	0.68666	0.57549	233.98	6.80
Δ (Prod. – React.)			-0.004	-0.001	-7.395	-2.208
Lys	-0.31119	0.32017	0.26075	0.20877	109.41	2.47
Lys+Dap	-0.22971	0.23990	0.49979	0.41138	186.07	4.41
Δ (Prod. – React.)			-0.002	0.001	-6.257	-4.598
2Lus+Dap	-0.22736	0.25154	0.72990	0.61188	248.40	4.72
Δ (Prod. – React.)			-0.004	0.000	-8.055	-5.048
Meth	-0.24910	0.31752	0.20712	0.15674	106.02	1.64
Meth+Dap	-0.22793	0.24125	0.44610	0.35924	182.81	5.41
Δ (Prod. – React.)			-0.002	0.001	-6.127	-2.768
2Meth+Dap	-0.22831	0.25041	0.62247	0.50756	241.84	5.96
Δ (Prod. – React.)			-0.004	0.000	-7.835	-2.148
Phe	-0.27248	0.26378	0.23105	0.18134	104.62	1.23
Phe+Dap	-0.22849	0.23860	0.46972	0.38205	184.51	6.40
Δ (Prod. – React.)			-0.002	0.000	-3.027	-1.368
2Phe+Dap	-0.22734	0.25147	0.67047	0.55640	240.08	6.45
Δ (Prod. – React.)			-0.004	-0.001	-6.795	-0.838

Pro	-0.30589	0.31697	0.17817	0.13734	85.94	1.73
Pro+Dap	-0.21527	0.24840	0.41714	0.33846	165.59	5.15
Δ (Prod. – React.)			-0.002	0.000	-3.267	-3.118
2pro+Dap	-0.25444	0.22422	0.56593	0.47149	198.76	2.65
Δ (Prod. – React.)			-0.003	0.002	-10.755	-5.638
Ser	-0.32190	0.31640	0.13917	0.09761	87.46	2.94
Ser+Dap	-0.22184	0.25275	0.37769	0.29824	167.23	5.31
Δ (Prod. – React.)			-0.002	-0.001	-3.147	-4.168
2Ser+Dap	-0.22720	0.25125	0.48669	0.38877	206.09	7.34
Δ (Prod. – React.)			-0.004	-0.001	-6.465	-3.368
Thr	-0.31895	0.31722	0.17390	0.12953	93.39	3.05
Thr+Dap	-0.22197	0.25242	0.41280	0.33150	171.12	5.48
Δ (Prod. – React.)			-0.002	0.001	-5.187	-4.108
2Thr+Dap	-0.23535	0.23760	0.55673	0.45477	214.59	7.12
Δ (Prod. – React.)			-0.003	0.001	-9.825	-3.808
Trp	-0.21066	0.23996	0.26610	0.21172	114.45	3.43
Trp+Dap	-0.21344	0.23697	0.50528	0.41419	191.71	7.39
Δ (Prod. – React.)			-0.001	0.001	-5.657	-2.578
2Trp+Dap	-0.21557	0.22761	0.74146	0.61898	257.78	11.39
Δ (Prod. – React.)			-0.003	0.001	-8.755	-0.298
Tyr	-0.24068	0.25928	0.23648	0.18391	110.64	0.60
Tyr+Dap	-0.22229	0.25244	0.47516	0.38519	189.35	4.42
Δ (Prod. – React.)			-0.002	0.000	-4.207	-2.718
2Tyr+Dap	-0.22826	0.25065	0.68160	0.56250	250.68	4.72
Δ (Prod. – React.)			-0.004	0.000	-8.235	-1.308
Val	-0.31282	0.31688	0.20373	0.15922	93.69	1.90
Val+Dap	-0.22199	0.25269	0.44226	0.36010	172.92	5.28
Δ (Prod. – React.)			-0.002	0.000	-3.687	-3.158
2Val+Dap	-0.22764	0.25111	0.61586	0.51274	217.04	6.67
Δ (Prod. – React.)			-0.004	0.000	-7.975	-1.958

The parameters of the examined prodrugs at their equilibrium geometries were calculated using the HF/STO-3G method, as shown in Table 1. The different data between the (product-reactant) were determined depending on the following equation:

Dapsone + Amino acid $\rightarrow$ Complex + H_2O

From Table 2. we can note that all the docking between dapsone with one molecule of amino acid is more favorite compared to the docking with two molecules of amino acid. Where the dipole moment, Gibbs free energy, and entropy like examples, had a small value compared to that with two molecules of amino acids.

3.1 Docking With Proteins

Various proteins were used to investigate docking with the dapsone molecules using (6WTT, 6XA4, 6XBG, 6XFN, and 7JRN) proteins. The effect of produced chemicals on proteins was investigated by simulations.

Table 3. Docking parameters between the proteins with dapsone

No.	Proteins	Score	E-conf
1	6WTT	-5.2727	35.6112
2	6XA4	-5.2740	37.4092
3	6XBG	-5.6240	39.1198
4	6XFN	-5.8502	39.2422
5	7JRN	-4.7346	36.2070

In Table 3. the docking of compound (4) has the greatest binding energy value when compared to the other proteins (-5.8502). The docking was shown to be more stable when one oxygen atom was in contact with two amino acids (Gly 143 and Cys 145) and one atom of amine was in contact with one amino acid (Glu 166) as shown in Fig 7. While less stable, the benzene ring was attached to one amino acid (Gln 189) as seen in Fig 8.

Also, one of the benzene rings for the dapsone molecule was attached to the (Met 165) by the aromatic ring. The other benzene ring for the dapsone has been linked to the (His 41) by the hydrogen bonding between them as shown in Fig 7 and 8.

In (Fig 11 & 12), there are two interaction between two amino acid (Glu166 and His 163) binding with two oxygen atoms which contains pairs of electrons on the oxygen atoms.
Also, (Met 165 and Thr 190) have been attached by a bond with electron pairs in the oxygen and with nitrogen respectively.

Two amino acids (Phe 127 and Lys 126) were bonded with electron pairs on the oxygen and with the double bonds in the aromatic ring respectively.

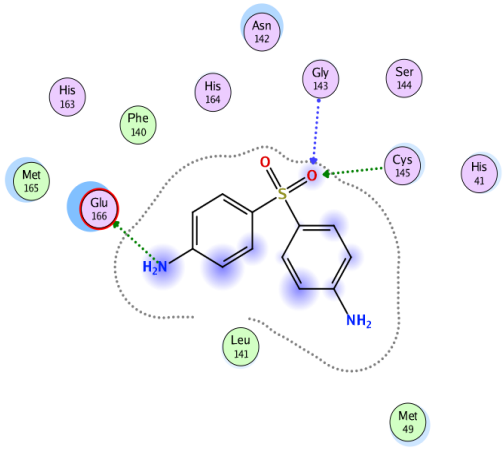

Figure 7. More stable of (6XFN) with dapsone

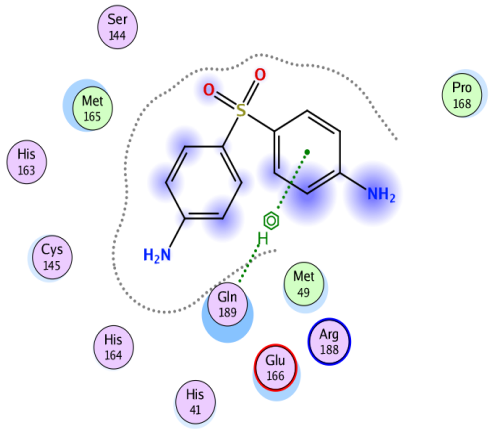

Figure 8. Less stable of (6XFN) with dapsone

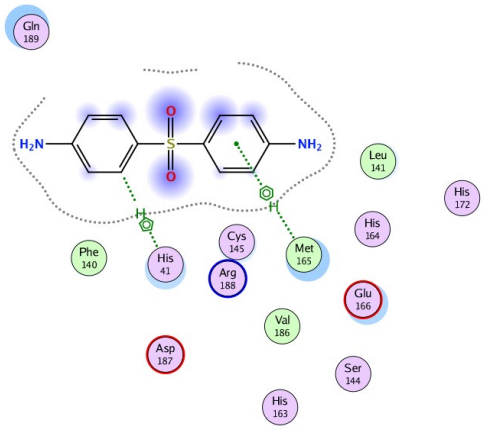

Figure 9. More stable of (6wtt) with dapsone

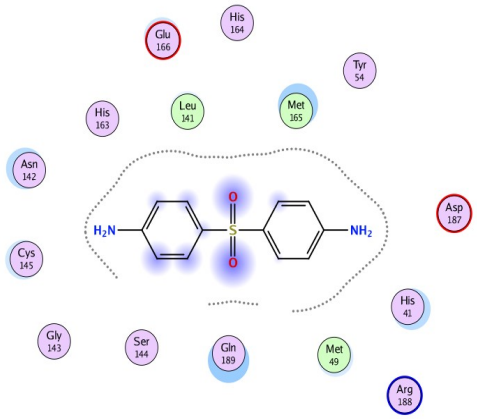

Figure 10. Less stable of (6wtt) with dapsone

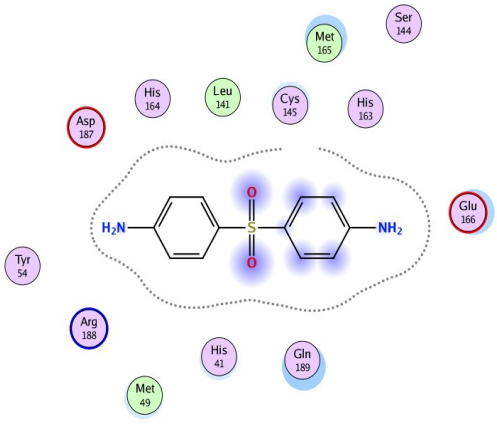

Figure 11. More stable of (6xa4) with dapsone

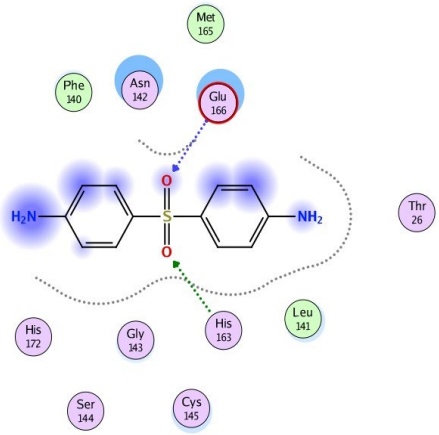

Figure 12. Less stable of (6xa4) with dapsone

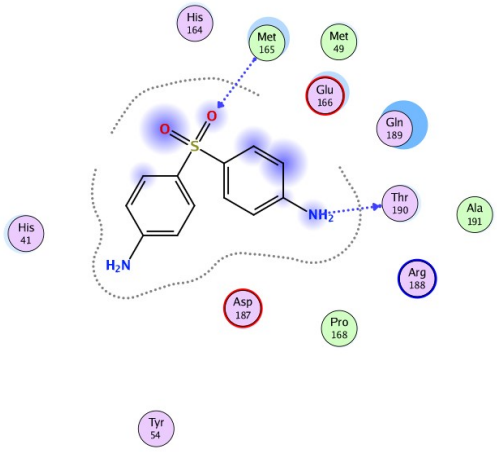

Figure 13. More stable of (6xbg) with dapsone

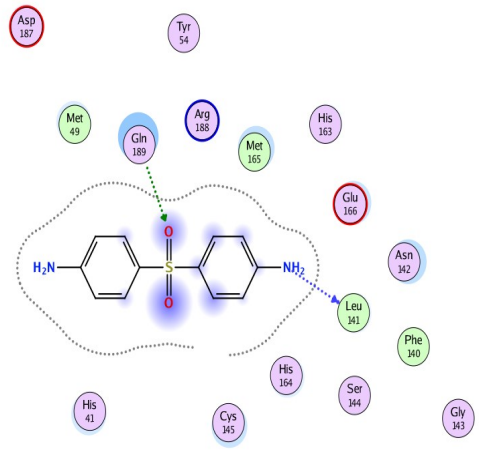

Figure 14. Less stable of (6xbg) with dapsone

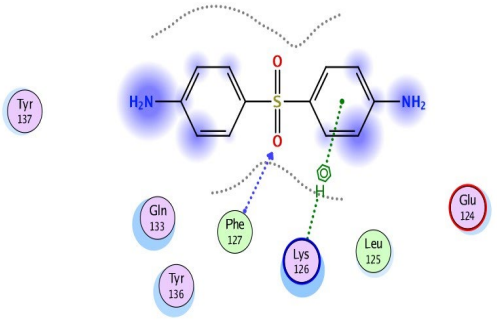

Figure 15. More stable of (7jrn) with dapsone

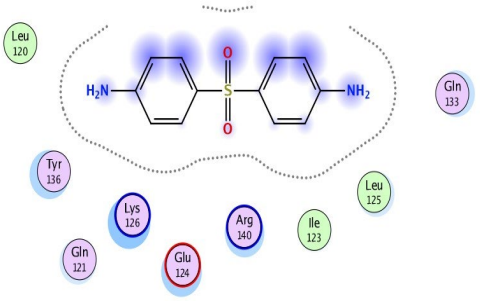

Figure 16. less stable of (7jrn) with dapsone

Finally, in comparing the binding of dapsone with the COVID-19 proteins we can note that in Fig 9. , the docking of dapsone with protein (4) was shown to be more stable than others for all of the proteins examined.

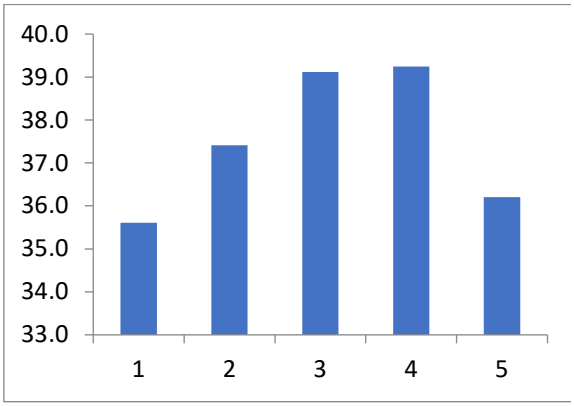

Figure 9. Comparison between the prodrug depends on the (E-conf) values

4. Conclusions

The COVID-19 virus has just been around for a few months. Bioinformatics and multi-target molecular modeling-driven in vitro anti-viral studies, as well as the repurposing of prior SARS-CoV protease inhibitors, are the practical techniques up till exact molecular and structural biology behind SARS-CoV-2 replication is accessible [28]. All the data of energy docking are less than from their reactant compounds. So, this means that the interaction docking between the dapsone and the amino acids is completed and the complexation is done. Also, this is the first research interesting to the determination of the energies of the interaction of dapsone with mono and di-amino acids to proceed with the product with aqua molecules evaluated. We can predict, or better still, suggest, targeting the allosteric regions of coronavirus proteases as a strategies-based drug discovery tool based on recent mechanistic and structural evidence on other viral proteases [29]. On the other side, the docking of dapsone with different proteins causes COVID-19 are calculated. The dapsone drug was docked with five proteins and the results showed that the (6XFN) protein has the best correlation by a more stable score.

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