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Docking of Drugs-Protein for COVID-19 and Prediction of pKa Using Quantum Calculations

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A B S T R A C T

For the computations of the compounds, the Gaussian 03 software has been applied utilizing (AM1), (HF), and density functional theory (DFT). Four medications have been theoretically assessed to anticipate the pKa values based on the calculations of HOMO, LUMO, ΔG, ΔH, and ΔS parameters. The prediction of the protein-drugs has been carried out using the docking studies. The docking simulations for the drugs with the receptor and parameterization were carried out using the molecular operating environment (MOE) software program. Theoretically, four medications were docked with the COVID-19 protein on a receptor (PDB ID: 6wtt). Four medications have been looked into virtually in an effort to find a possible anti-COVID molecule. The drugs have been molecularly docked with the covid-19 protein (6wtt).

Introduction

The pKa is a crucial physical characteristic to consider while developing new drugs. The pKa value is used to describe an acid's potency. Stronger acids more completely dissociate in water when the pKa value is lower[1]. Drug molecules' pKa values offer crucial details regarding their physicochemical and pharmacological characteristics. In authorized medications, a wide range of basic and acidic pKa values, ranging (0-12), have been seen. The pKa is an important physical property to take into account in drug development. The pKa value is used to indicate the strength of an acid. A lower pKa value indicates a stronger acid, indicating the acid more fully dissociates in water[2].

Compared to simple monoprotic compounds, drug-like molecules pose difficulties for pKa prediction. Drug-like compounds usually have extensive conjugated systems, are multiprotic, commonly feature heterocycles, and have the ability to tautomerize[3]. In contrast to molecules that are unable to create intra-molecular hydrogen bonds, drug-like compounds with high conformational flexibility may establish intra-molecular hydrogen bonds, which can drastically change their pKa values[4].

Numerous theoretical physical characteristics have been calculated for 10 derivatives of carboxylic compounds using various techniques. Using several forms of regression, the estimated data were associated with experimental values of pKa. The prediction values were obtained using multiple linear regression utilizing the enter approach in comparison to the stepwise method, and the two methods outperformed simple regression[5]. A significant physicochemical factor that affects several biopharmaceutical features is a drug's (pKa) values. The overall ratio of non-ionizable and ionizable molecules for drug-like substances has been thoroughly established. The pharmacokinetics of medicine are directly impacted by the solubility, permeability, lipophilicity, and binding of the drug. [6].

The log P is commonly defined as the equilibrium concentration ratio of a substance's neutral state between two phases. Drug discovery is important to the partition coefficient (log P), which is used to define lipophilicity. Through hydrophobic interactions, lipophilicity affects medication target interactions. Relatively high lipophilicity reduces water solubility and increases the chance of metabolic instability[7,8]. The biggest difficulty the globe is facing in December 2019 is COVID-19, particularly in China. Worldwide, COVID-19 infections and fatalities are at an extremely high and steadily rising level. Consequently, developing therapeutic or preventative medications or vaccinations is the final and only way to survive the pandemic. Docking is used to determine the target bio-macromolecules and the small molecule's mode of action[9,10].

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 to be a pandemic. Numerous medication trials are ongoing, and some of the outcomes are promising. However, as there is currently no vaccine for the virus, prevention measures are the most effective treatment[11-13]. Due to its efficiency and safety, chloroquine, which is often used to treat malaria, is intriguing in the treatment of COVID-19. Natural products [14] and hydroxychloroquine [15] can be utilized as a preventative measure as well as a treatment for corona patients because of their strong binding affinity for COVID-19 protease [16-18]. It is critically necessary to create a particular curative medication, preventative measure, or vaccination to treat COVID-19. The diverse antibacterial and antiviral activity of sulfonamide derivatives against many pathogens has earned them fame [19].

The docking outcome demonstrated a significant affinity of certain medications to the new coronavirus 6LU7 receptor. As a result, the combination of these medications may help to stop the spread of infection and can be utilized as a possible target for additional in vitro and in vivo research of SARS-CoV-2 [20]. SARS-CoV-2 was used to study medications using docking simulations to comprehend processes. Recent investigations employing computational modeling techniques described the theoretical calculations for COVID-19 protease with several therapeutic medications [21].

Through potential effects on processes, the drugs/molecules can be turned into potential therapeutic candidates for COVID-19 therapy by taking a closer look at various pathways of COVID-19 diseases involving host proteins [22]. Medicines underwent computational prediction of the interaction[23]. The physical characteristics of these medicinal molecules and their complexation with alanine have been studied using semi-empirical, Hartree-Fock, and DFT [24]. The impact of curcumin, a naturally occurring bioactive chemical, on

COVID-19, is being investigated since it has been demonstrated to have therapeutic promise for many disorders. Curcumin's ability to bind to several SARS-CoV-2 proteins was assessed [25].

Experimental Methods:

The characteristics of the starting chemicals and the produced products were assessed using theoretical simulations. Through (AM1), Hartree-Fock (HF) at basis sets (STO-3G and 6-31G), and DFT with B3LYP functional at 6-31G basis set in gaseous state, all the structures of pharmaceuticals have been energy minimized using Gaussian (03) software. For the COVID-19 protein docking computations, optimal structures were employed (PDB ID: 6WTT). All docking calculations use the molecular operating environment (MOE). The (MOE) has been used to prepare the structures of proteins and small molecules.

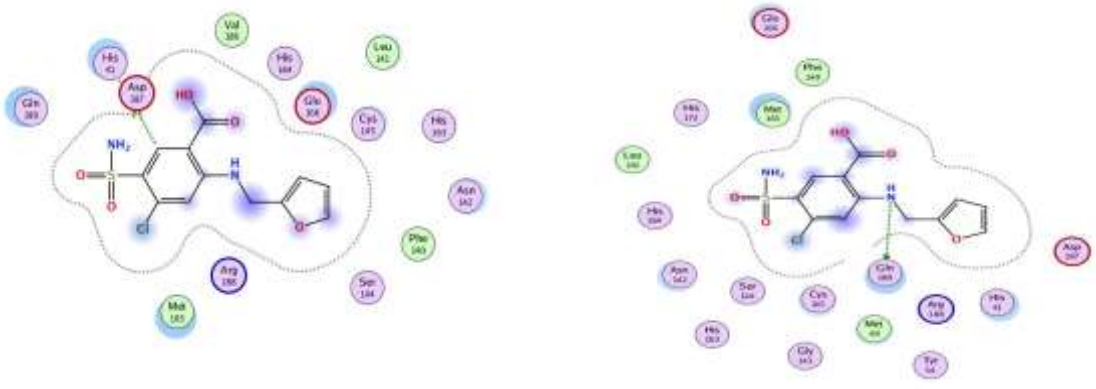
The compounds' 2D structures were first generated and then transformed into 3D structures, which were subsequently energetically minimized using the Gaussian (MOE) software.

Results and Discussion:

Docking with (6wtt):

The number of the receptor of protein (6wtt) was (2326) atoms which contain (1470) of carbon, (397) of nitrogen, (437) of oxygen, and (22) of sulfur atoms. The hydrophobic, charged, and Van der Waals interactions between the ligand and receptor molecules served as evidence of the binding. By choosing COVID-19 major protease as the receptor molecule and medication as the ligand molecule in the (MOE) software tool, docking tests were carried out and the docking score was determined. After the docking procedure was completed, a docked complex was generated, and the interaction between the ligand and receptor molecule was then determined.

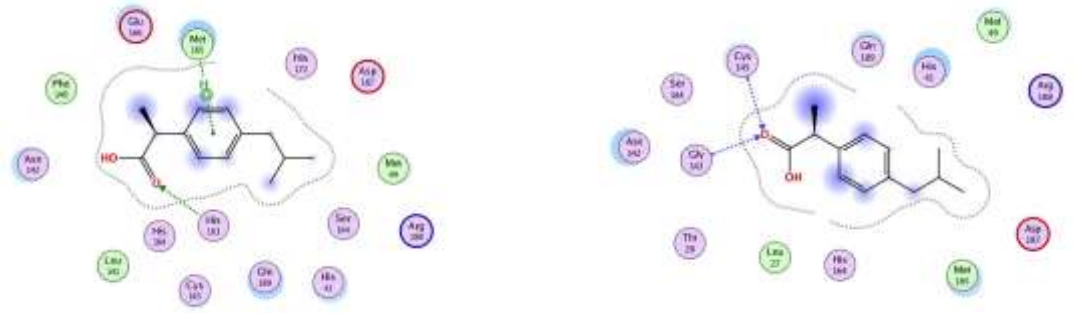
We picked four medications to test for COVID-19 inhibitory activity. For the treatment of COVID-19, we compare each medication to previously prescribed medications such as furosemide, ibuprofen, imipramine, naproxen, piroxicam, progesterone, and propranolol. The more stable (His 41) and (Asp 187) of the aromatic ring where the furosemide was joined by hydrogen, whereas the less stable (which had connected between the amide (-NH) with (Gln 189).



More stable Less stable

Figure 1: Docking of the drug (furosemide) with the protein (6wtt)

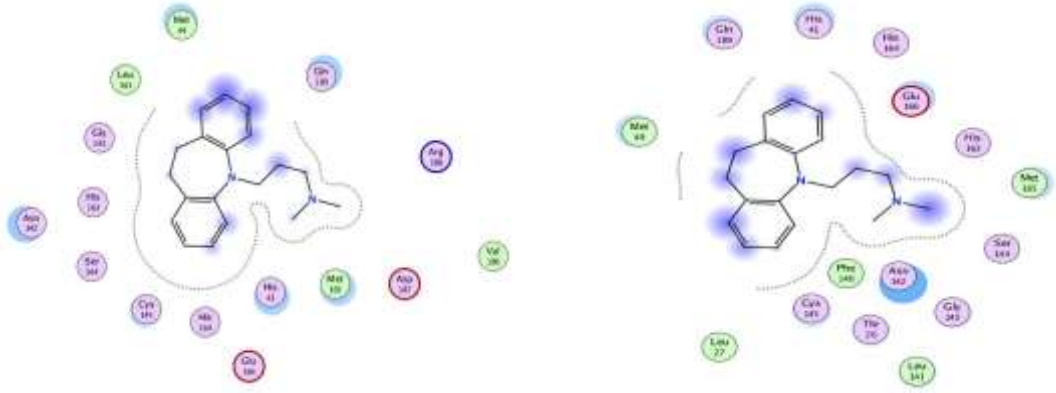
Ibuprofen's medicinal component was made more stable by connecting the hydrogen in the aromatic ring (Met 165). When compared to the less stable, the oxygen was bound with (Cys 145 and Gly 143).



More stable Less stable

Figure 2: Docking of the drug (Ibuprofen) with the protein (6wtt)

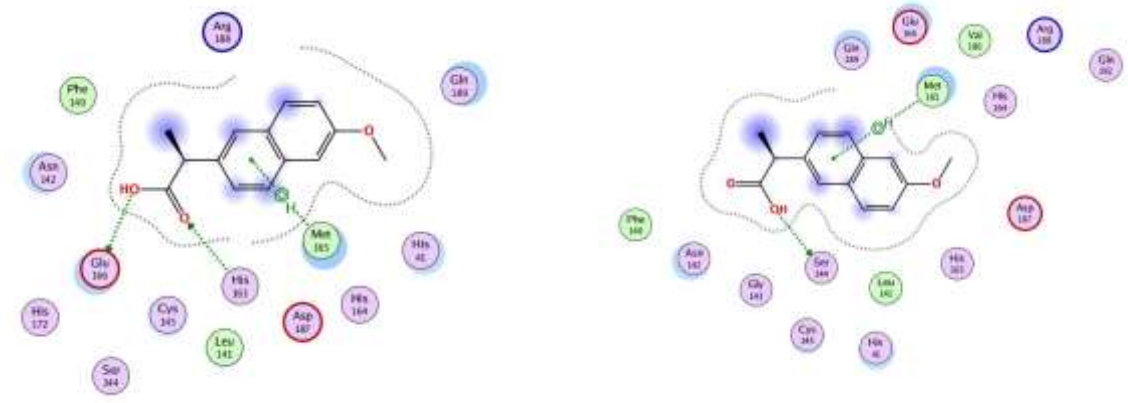
While the aromatic ring was active when close to the imipramine structure, we obtained the more stable (Gln 189 and Met 49). On the other hand, this medication was less stable when there were a lot of amino acids close to the aromatic ring in the molecule.



More stable Less stable

Figure 3: Docking of the drug (imipramine) with the protein (6wtt)

The drug naproxen exhibits two active group binding. When the molecule is bound to the active site by interacting with the hydrogen in the aromatic ring, it is discovered to be more stable (Met 165). Additionally, binding for the aromatic ring's oxygen atom with (His 165) and the hydroxyl atom with (Glu 166) correspondingly. In the less stable form, the binding was established between the hydroxy with (Met 165) and the hydrogen in the aromatic ring with (Ser 144).



More stable Less stable

Figure 4: Docking of the drug (naproxen) with the protein (6wtt)

According to the graph (5) and table (1), furosemide has the greatest binding score value (-6.5040569). The molecule's main method of binding is hydrogen bonding. With the help of the inhibitor (6wtt), the free (NH2), (SO2), and amide (-NH) were increased to hydrogen confined state.

Table 1: Summary of data from docking between drugs with protein

No.	Drugs+6wtt	score	
		more stable	less stable
1.	Furosemide	-6.5040569	-6.129595
2.	Ibuprofen	-5.9001074	-5.616890
3.	Imipramine	-5.9510899	-5.790836
4.	Naproxen	-5.9068484	-5.775814

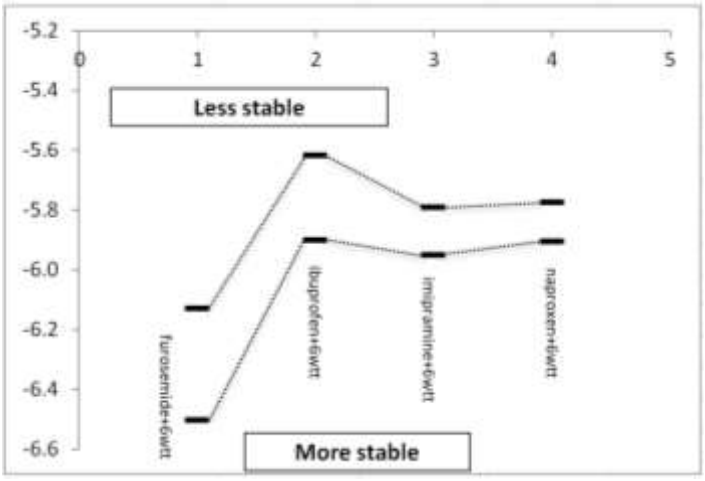


Figure 5: Scheme of the less and more stable of the docking

Prediction of log K:

These calculations aim to forecast pKa values and the ratio of bases to acids in a drug development environment. All drugs depict a selection of typical acids and bases that comprise different aromatic, heterocycle, hydroxy, and amine compounds. the physical characteristic that concentrated on pKa values for the group of drugs. The pH level at which the corresponding acid and its conjugate base are each equally populated in solution is indicated by the pKa value.

Five physical parameters from quantum molecular chemistry, including HOMO, LUMO, ΔH, ΔG, and ΔS, were utilized to determine the characteristics of medicines. In tables (2-5), the two techniques (enter and stepwise), which indicate projected performance in these values, are compared with experimental pKa and predicted values using different methods.

Table 2: The physicochemical characteristics of drugs utilizing by (AM1) method

Name	log Kp (exp.)	HOMO (a.u)	LUMO (a.u)	ΔH (a.u)	ΔG (a.u)	ΔS cal/mol-K	Prediction (Enter)	Prediction (stepwise)
imipramine	4.39	-0.28978	0.00978	0.419782	0.350428	145.968	4.45	4.42
propranolol	3.48	-0.30295	-0.01664	0.369404	0.300653	144.698	3.59	3.52
ibuprofen	4.13	-0.34331	0.01082	0.305546	0.242813	132.033	4.24	4.15
naproxen	3.24	-0.31852	-0.02841	0.273283	0.21033	132.495	3.23	3.07
furosemide	2.56	-0.30638	-0.04749	0.254526	0.182708	151.155	2.55	2.54
piroxicam	1.98	-0.32499	-0.05909	0.295165	0.224179	149.403	2.13	2.07
progesterone	3.89	-0.364	0.00626	0.503787	0.433959	146.965	3.91	3.89

Using experimental log K values from seven different drugs, SPSS software created a multi-linear regression (MLR) approach using (Enter) and (stepwise) methods. The HOMO, LUMO, ΔH, ΔG, and ΔS descriptors were utilized to generate the MLR. Thus, the pKa parameters for every drug molecule were calculated using these parameters as input. We discover that predictions for the two techniques are quite close to being correct with correlation coefficient when we take into account the computed of each molecule by two method categories (Enter and Stepwise).

Enter Method:

Log K =7.299+(6.315*HOMO)+(29.218*LUMO)+ (0.449*ΔG)-(0.01*ΔS) ---- (R=0.997)

Stepwise Method:

logK =5.742+(31.169*LUMO)+(5.617*HOMO) ---- (R= 0.995)

The (Enter) technique demonstrates that in contrast to (Stepwise), which was impacted by HOMO and LUMO, the (log K) was affected by HOMO, LUMO, ΔG, and ΔS. These outcomes (Enter method) were displayed in the (AM1) and (HF/STO-3G), (HF/6-31G) and (DFT-STO3-G).

Table 3: The physicochemical characteristics of drugs utilizing by (HF/STO-3G) method

Name	log Kp (exp.)	HOMO (a.u)	LUMO (a.u)	ΔH (a.u)	ΔG (a.u)	ΔS cal/mol-K	Prediction (Enter)	Prediction (stepwise)
imipramine	4.39	-0.18803	0.25139	0.479794	0.413544	139.434	4.36	4.31
propranolol	3.48	-0.19582	0.20022	0.420461	0.353706	140.498	3.53	3.48
ibuprofen	4.13	-0.25778	0.26495	0.350823	0.29153	124.792	4.19	4.21
naproxen	3.24	-0.21297	0.18518	0.306751	0.248015	123.621	3.28	3.17
furosemide	2.56	-0.07313	0.10952	0.275511	0.203237	152.114	2.64	2.61
piroxicam	1.98	-0.22863	0.11336	0.32247	0.253533	145.089	1.98	1.97
progesterone	3.89	-0.27741	0.25157	0.584776	0.517463	141.671	3.97	3.92

Enter Method:

logK =2.799+(5.356*HOMO)+(13.939*LUMO)+ (1.103*ΔG)-(0.01*ΔS) ---- (R= 0.999)

Stepwise Method:

logK =1.226+(15.649*LUMO)+(4.497*HOMO) --- (R= 0.998)

Table 4: The physicochemical characteristics of drugs utilizing (HF/6-31G) method

Name	log Kp (exp.)	HOMO (a.u)	LUMO (a.u)	ΔH (a.u)	ΔG (a.u)	ΔS cal/mol-K	Prediction (Enter)	Prediction (stepwise)
imipramine	4.39	-0.25825	0.13354	0.441701	0.374674	141.07	4.29	4.30
propranolol	3.48	-0.26843	0.08887	0.388972	0.323633	137.518	3.47	3.40
ibuprofen	4.13	-0.31784	0.13165	0.322448	0.263375	124.33	4.09	4.27
naproxen	3.24	-0.28547	0.06993	0.286159	0.227673	123.095	3.16	3.02
piroxicam	1.98	-0.30499	0.02544	0.308569	0.238588	147.287	1.91	2.12
progesterone	3.89	-0.34674	0.11819	0.530335	0.462337	143.114	3.82	3.99

Enter Method:

logK =5.053+(4.208*HOMO)+(16.44*LUMO) +(2.168*ΔG)-(0.019*ΔS) --- (R= 0.999)

Stepwise Method:

Log K=1.611+(20.163*LUMO) --- (R= 0.985)

Table 5: The physicochemical characteristics of drugs utilizing (DFT/STO-3G) method

Name	log Kp (exp.)	HOMO (a.u)	LUMO (a.u)	ΔH (a.u)	ΔG (a.u)	ΔS cal/mol-K	Prediction (Enter)	Prediction (stepwise)
imipramine	4.39	-0.087	0.08469	0.442624	0.374805	142.737	4.43	4.34
propranolol	3.48	-0.09986	0.04975	0.387183	0.324248	132.458	3.65	3.32
ibuprofen	4.13	-0.13078	0.08439	0.323077	0.261837	128.889	4.21	4.33
naproxen	3.24	-0.13045	0.03706	0.281691	0.22153	126.62	3.06	2.95
piroxicam	1.98	-0.10422	0.01614	0.294469	0.223316	149.753	2.19	2.34
progesterone	3.89	-0.12527	0.06995	0.536309	0.464486	151.164	3.82	3.91

Enter Method:

Log K=5.613+(6.734*HOMO)+(23.718*LUMO)+(2.191*ΔG)-(0.024*ΔS) --- (R= 0.987)

Stepwise Method:

logK =1.872+(29.164*LUMO) --- (R= 0.967)

Conclusion:

Currently, there is a critical need for particular medications to treat certain conditions. COVID-19 is difficult to treat because recombination events occur often. Because it is a potent inhibitor of the COVID-19 main protease and exhibits good binding affinity with the macromolecule with a very good docking score and various binding interactions, theoretical chemistry, such as molecular docking, has led to the conclusion that the prediction of medicines may act as a preventive drug for the treatment of this pandemic.
Therefore, it is evident that the pKa values of a drug are essential, and understanding pKa distributions will help us identify and create novel medications and optimize the docking process with inhibitors.

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