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Theoretical Prediction of Possible Drug Treatment of COVID-19 using Coumarins Containing Chloroquine Moeity

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Chloroquine was theoretically reacted with the coumarin compound. Two compounds *viz*. [N-(7-chloroquinolin-4-yl)-N-(5-(diethylamino)-pentan-2-yl)-4-methyl-2-oxo-2*H*-chromene-7-sulfonamide] (**3**) and [N-(7-chloroquinolin-4-yl)-N-(5-(diethylamino)pentan-2-yl)-4-methyl-2-oxo-2*H*-chromene-6-sulfonamide] (**4**) were suggested. The results showed that compound **4** may influence the COVID-19 treatment. The physico-chemical parameters were determined through theoretical calculations by using Hartree-Fock at different basis sets (6-31G), (STO/3G) and the semi-empirical (AM1) method. The calculations demonstrated the scheme of reaction between coumarin and the chloroquine structure by using the predicted mechanisms. The physical and chemical properties of the predicted compounds were determined to select the optimal form as the candidate for COVID-19 treatment. Compound **4** was more stable than compound **3**, with different proteins *viz*. 6YHU, 6YI3 and 6LU7. Three types of software, including Gaussian 03, Chem-Bio office and molecular operating environment (MOE) were employed.

Keywords: COVID-19, Docking, Chloroquine, Coumarin.

INTRODUCTION

In December 2019, in China, especially in the Wuhan city, the novel coronavirus was first detected, which proved to be a deadly virus for humans [1]. In human patients, several symptoms appeared with respect to COVID-19, include cough, fever and difficultly in breathing. Additionally, some patients, especially geriatric patients and children, experience pain, languor, sore throat and runny nose. These symptoms can appear within 2-14 days after being infected. The symptoms of symptoms are similar to those of influenza. However, the medicine for the COVID-19 treatment has not yet been discovered, which causes patient death. COVID-19 rapidly spreads through air and direct or indirect contact with patients with this disease. Thus, in March 2020, World Health Organization declared the coronavirus (COVID-19) spread as pandemic [2]. According to the WHO report provided on 30 November 2020, the confirmed number of COVID-19 cases was more than 62 millions, while the number of deaths was < 14.5 millions [3].

Chloroquine, which is generally used for the treatment of malaria, has been found interesting in the treatment of for COVID-19 due to its effectiveness and safety [4-8]. More than 10,000 substituted coumarin compounds, which are obtained naturally especially from plans are isolated and characterized. Coumarin derivatives are highly crucial and used in the synthesis of antioxidant agents [9], perfumes [10], antifungal [11], anti-Alzheimer [12], anti-amnesic [13], pharmaceuticals [14] and antimicrobial activity [15]. In this study, two novel derivatives of chloroquine were synthesized theoretically when the reaction was conducted with coumarin. The theoretical calculations were employed to evaluate the properties of the synthesized products and the starting compounds. Three drugs were investigated through docking simulations by using SARS-CoV-2 to understand mechanisms. Recently, several studies [16-25] reported the theoretical calculations for COVID-19 protease with some medicinal drugs using computational modeling strategies.

EXPERIMENTAL

Synthesis of coumarin: The ethyl acetoacetate (0.1 mol) was mixed with phenol (0.1 mol) at 50 ºC followed by the addition of 45 mL sulphuric acid dropwise in a dry and cooled

100 mL round flask with magnetic stirring. The reaction mixture was cooled to below 10 ºC and subsequently, a water bath was raised, and stirring was continued for 1 h until the solution became thick. The crude was added to a beaker containing certain amount of ice while stirring and then subsequently filtered. The precipitate was washed several times using water until to remove acid and recrystallized with absolute ethanol.

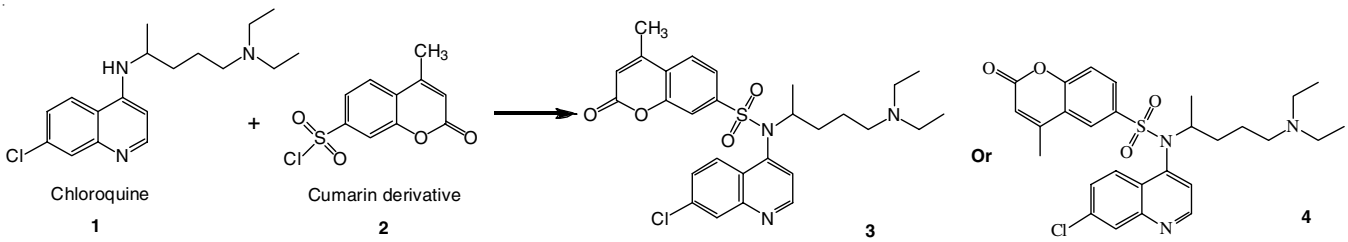
Synthesis of coumarin sulphonyl chloride: Chlorosulphonic acid was employed as the solvent and sulphonate agent with the slow and gradual addition of 1 mol of coumarin to a round flask at -8 ºC and was stirred magnetically. Subsequently, the mixture allowed to stand for 18 h. The mixture was heated using an oil bath to 100 ºC for 2-3 h. The mixture was cooled and then added to a beaker containing appropriate amount of ice. Stirring was continued until the precipitate was formed. Subsequently, the precipitate was separated through filtration and washed several times using cold water. Finally, the precipitate was recrystallized using aqueous ethanol (**Scheme-I**).

DFT Calculations: The physico-chemical properties of the predicted structures were theoretically determined through quantum calculations. Hartree Fock (STO-3G and 6-31G) and semi-empirical (AM1) methods were employed using Gaussian 03 software [26]. In the proposed reaction, first, structures were optimized through molecular mechanics. Subsequently, the Hartree Fock and semi-empirical methods were employed. For this predicted reaction, eigen values (HOMO and LUMO energies) are the optimum critical parameters. All the calculations were performed in the gas phase. The steric energy, Log P parameters and molar refractivity were analyzed using Chem Bio Office Ultra version (13.0) in the gaseous phase by employing molecular mechanics.

The MOE software package version 2009 was employed for docking studies [27]. Proteins were selected from the protein database bank. The docking procedure was conducted by adding hydrogen, removing water molecules and undesirable small proteins.

RESULTS AND DISCUSSION

All the optimized compounds (**1-4**, Fig. 1) are stable and approved in terms of the absence of the imaginary frequency.



Scheme-I: Proposed reaction of chloroquine (**1**) with cumarin derivative compound

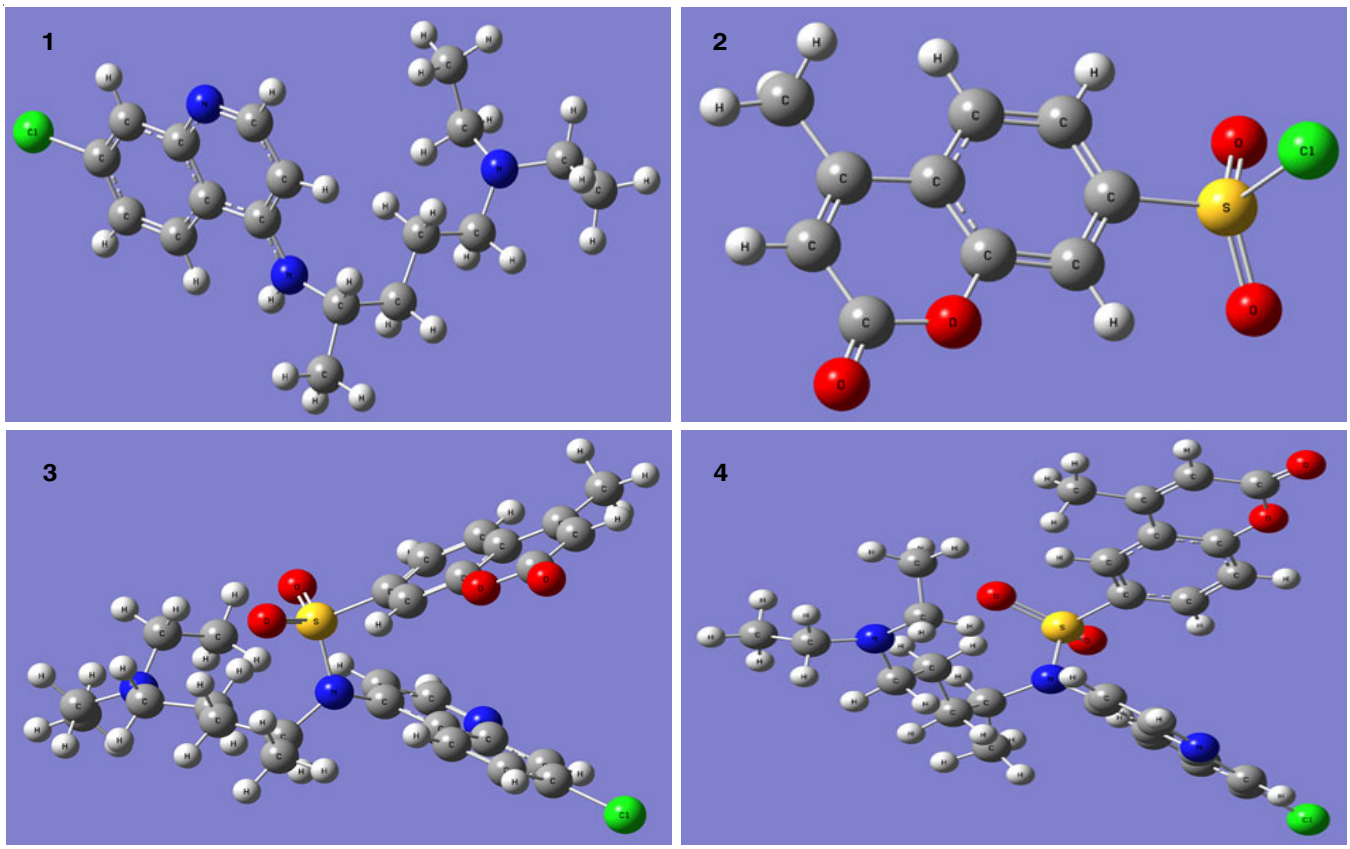


Fig. 1. Optimized structures of the compounds **1-4**

The stability and conductivity states were theoretically determined depending on differences in the energies (DE) between LUMO and HOMO. From the two energies (HOMO and LUMO), several parameters such as electron affinity, ionization potential, hardness, electronegativity and softnessare investigated. Thus, the high difference between HOMO and LUMO indicated that charge transfer was inconsiderable or absent.

Two plausible mechanisms are possible for the formation of two active compounds (**Scheme-I**). One is the attachment at the amino group in chloroquine having a coumarin derivative and second when the phosphate compound was replaced in the attachment. Table-1 provides some important information regarding the theoretical synthesized and the starting compounds, which were calculated through the Chem Office Ultra version 13.0. The refractivity and Log P values were the same for compounds **3** and **4** (Table-2). They exhibited the same conformation but have different configurations. The steric energy of compound **4** is lower than that of compound **3** (~5.2 kJ/mol).

TABLE-1
PARAMETERS EVALUATED BY CHEM BIO OFFICE SOFTWARE

Compd. No.	Steric energy (kJ/mol)	log P	Mol. refractivity
1	101.5460	3.726	9.568
2	834.4151	1.733	6.055
3	975.3322	4.890	14.890
4	970.1859	4.890	14.890

Table-3 listed the values of the several thermodynamic parameters *viz*. entropy, enthalpy, free energy, total energy, heat of formation and also the energy at various levels for the two synthesized compounds and the reactants. All these parameters were calculated using Gaussian 03 [27]. From the calculated methods, ΔG values indicated that the formation of compound **4** was better than compound **3**. However, in the AM1 method, the LUMO-HOMO gap favoured compound **4**, while compound **3** was favoured by other methods.

The difference between LUMO and HOMO energies obtained from the AM1 method was approximately 0.4287 and 0.296 for compounds **3** and **4**, respectively (Fig. 2). The energy gap for compound **3** was lower than that for compound **4** (Figs. 3 and 4). By contrast, the electrophilicity of a compound is a crucial factor for deciding the favourable structure. Hence, the electrophilicity for compound **3** is less than for compound **4** (Fig. 4).

Docking studies: Docking between the two synthesized compounds was studied with various proteins rings: 6YHU, 6YI3 and 6LU7 (Figs. 5-7). Simulation studies were performed to investigate the effect of synthesized compounds on proteins. It is found that compound **4** is more stable for all the studied proteins than compound **3** (Table-4).

Conclusion

Two novel compounds synthesized theoretically from antimalarial drug, chloroquine and coumarin has been investigated

TABLE-2
PHYSICO-CHEMICAL PARAMETERS CALCULATED BY GAUSSIAN 03

	ΔG (Reaction)		ΔH (Reaction)		LUMO-HOMO	
	3	**4**	**3**	**4**	**3**	**4**
AM1	0.09719	0.01724	0.06552	-0.01374	0.42873	0.29621
HF/STO-3G	0.01418	0.01309	-0.01464	-0.01468	0.42873	0.43454
HF/6-31G	0.01598	0.01512	-0.01297	-0.01330	0.35509	0.37530

TABLE-3
PHYSICO-CHEMICAL PARAMETERS USING AM1, HF/STO-3G AND HF/6-31G METHODS

	AM1 method				HF/STO-3G method				HF/6-31G method			
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
HOMO	-0.31420	-0.37650	-0.26493	-0.34276	-0.23520	-0.27516	-0.26493	-0.26701	-0.29262	-0.37092	-0.32755	-0.33681
HOMO-1	-0.33654	-0.39608	-0.26616	-0.34683	-0.28116	-0.31019	-0.26616	-0.27069	-0.32291	-0.39758	-0.33776	-0.34031
HOMO-2	-0.34818	-0.43391	-0.27808	-0.36073	-0.28398	-0.31514	-0.27808	-0.28533	-0.33822	-0.46496	-0.35571	-0.35640
HOMO-3	-0.36601	-0.44835	-0.28740	-0.36689	-0.31048	-0.32073	-0.28740	-0.28939	-0.36329	-0.46987	-0.35947	-0.35943
LUMO	-0.01687	-0.08728	0.16380	-0.04655	0.19221	0.10836	0.16380	0.16753	0.08756	-0.03991	0.02754	0.03849
LUMO+1	-0.00668	-0.06954	0.17526	-0.04382	0.22310	0.16989	0.17526	0.17005	0.11622	0.02865	0.04684	0.04431
LUMO+2	0.03546	-0.03121	0.21241	-0.03716	0.29825	0.21751	0.21241	0.20112	0.18212	0.08160	0.09001	0.06773
LUMO+3	0.04940	-0.01813	0.22655	-0.02580	0.35336	0.25293	0.22655	0.20975	0.18237	0.10430	0.09660	0.09005
E	0.42173	0.15987	0.65035	0.57090	0.48887	0.17396	0.65035	0.650228	0.44749	0.16554	0.60234	0.60194
ΔE	0.44437	0.17380	0.68464	0.60537	0.51002	0.18832	0.68464	0.684596	0.46916	0.17923	0.63637	0.63604
ΔH	0.44532	0.17474	0.68558	0.60632	0.51096	0.18926	0.68558	0.68554	0.47011	0.18017	0.63731	0.63698
ΔG	0.36475	0.11741	0.57935	0.49940	0.43433	0.13084	0.57935	0.578261	0.39249	0.12374	0.53220	0.53134
E (thermal) (Kcal/mol)	278.85	109.06	429.62	379.88	320.04	118.17	429.62	429.59	294.40	112.47	399.33	399.12
CV (Cal/mol-K)	83.13	51.42	125.98	129.50	76.81	51.69	125.98	125.919	79.84	50.77	127.75	127.78
S (Cal/mol-K)	169.57	120.66	223.57	225.03	161.28	122.95	223.57	225.787	163.37	118.79	221.21	222.33
HF	0.04	-0.16	-2370.08	-0.08966	-1304.28	-1520.97	-2370.09	-2370.08	-1319.22	-1538.63	-2397.80	-2397.81
Chemical potential	-0.13937	-0.20386	-0.02626	-0.18996	0.03153	-0.02883	-0.02626	-0.03295	-0.05525	-0.14466	-0.11877	-0.13454
Hardness	0.17483	0.17265	0.23867	0.15280	0.26673	0.24634	0.23867	0.23407	0.23737	0.22626	0.20878	0.20227
Softness	0.82517	0.82736	0.76133	0.84720	0.73328	0.75367	0.76133	0.76594	0.76263	0.77374	0.79122	0.79773
Electro-philicity	5.555×10^{-2}	1.204×10^{-1}	1.445×10^{-3}	1.181×10^{-1}	1.863×10^{-3}	1.686×10^{-3}	1.445×10^{-3}	2.319×10^{-3}	6.430×10^{-3}	4.624×10^{-2}	3.378×10^{-2}	4.474×10^{-2}

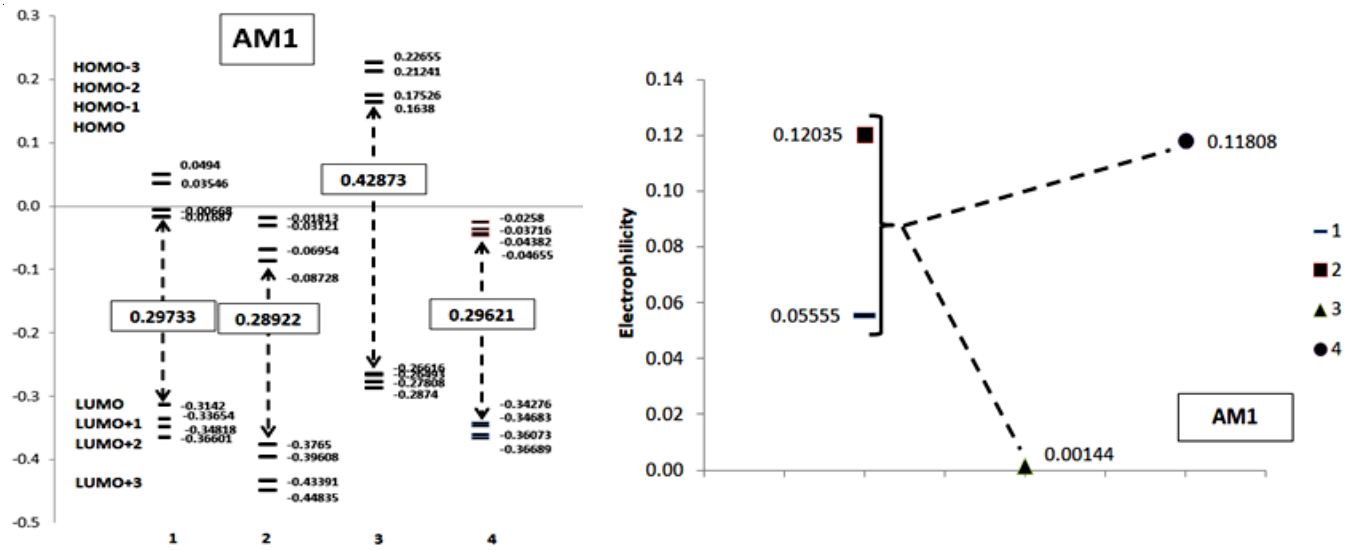


Fig. 2. Energy gap and electrophilicity for all compounds using AM1 method

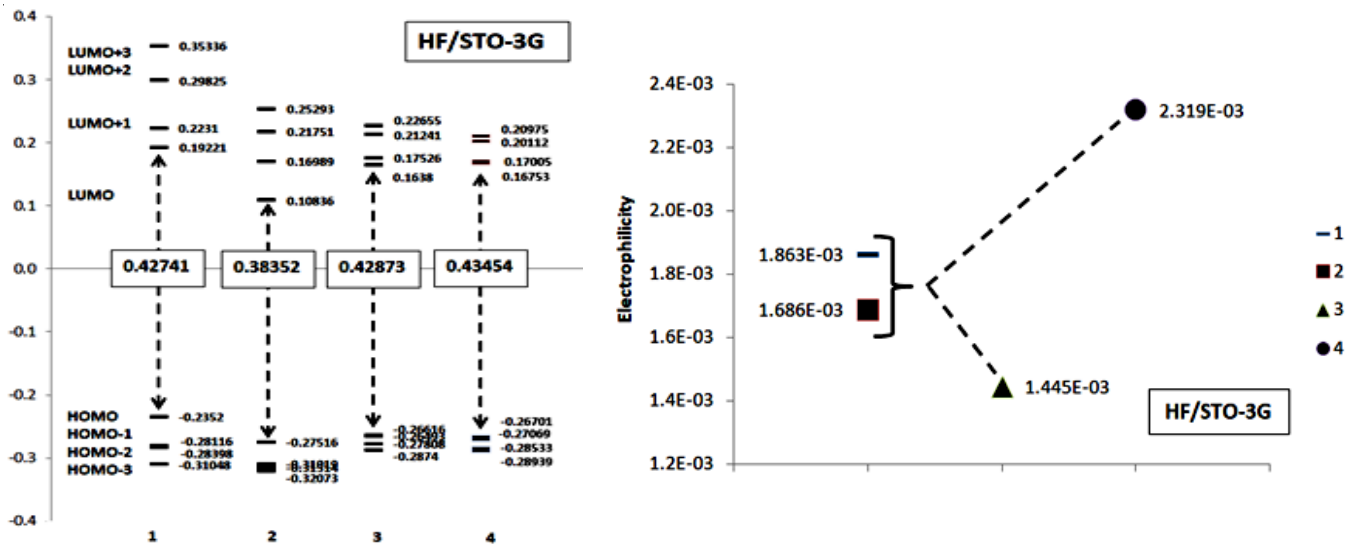


Fig. 3. Energy gap and electrophilicity for all compounds using HF/STO-3G method

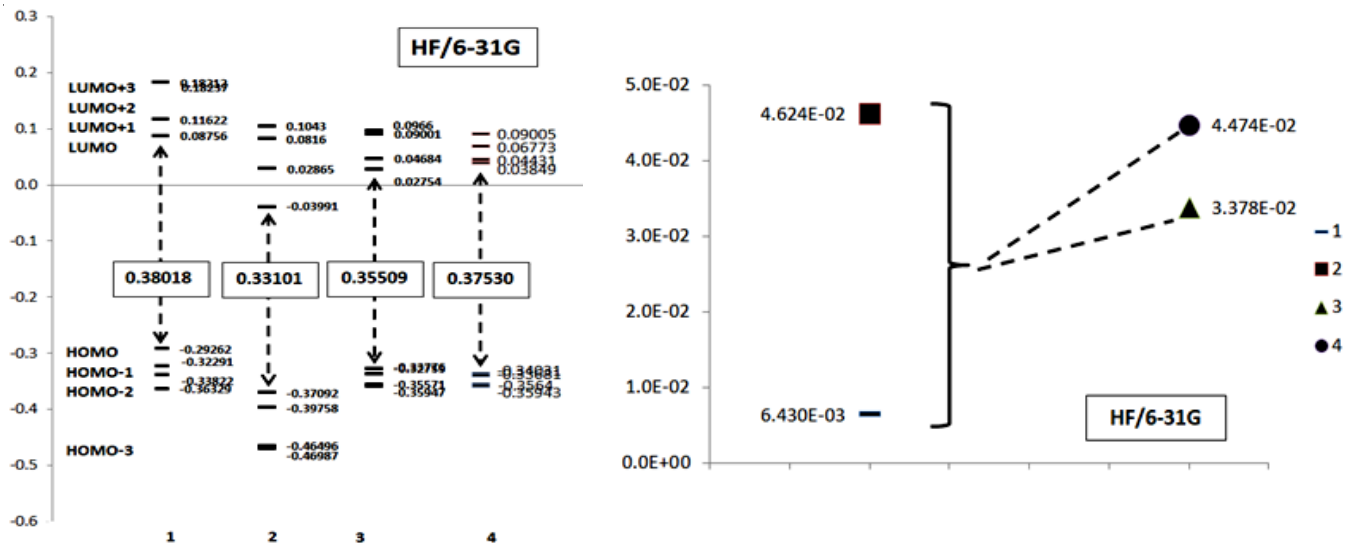
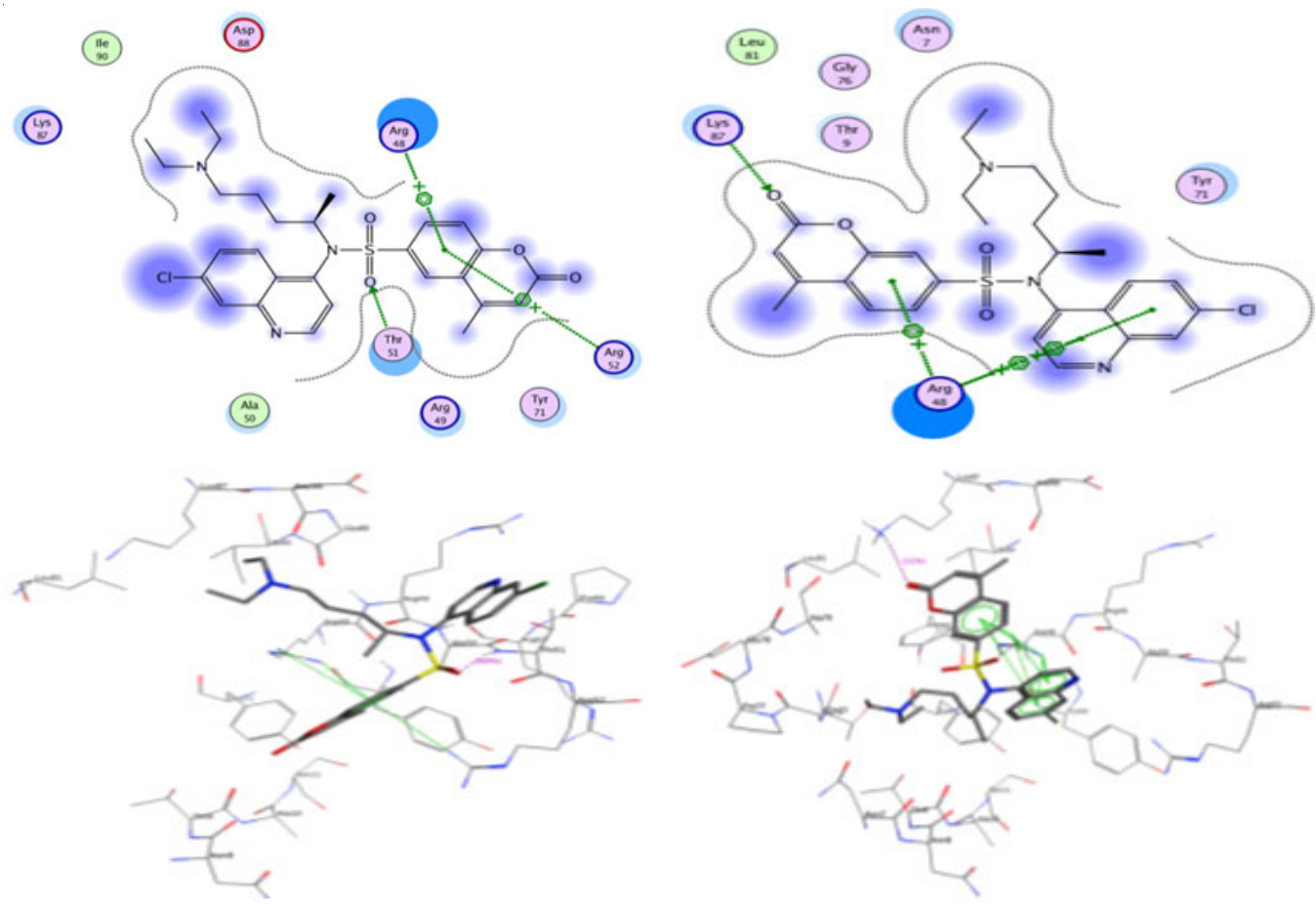
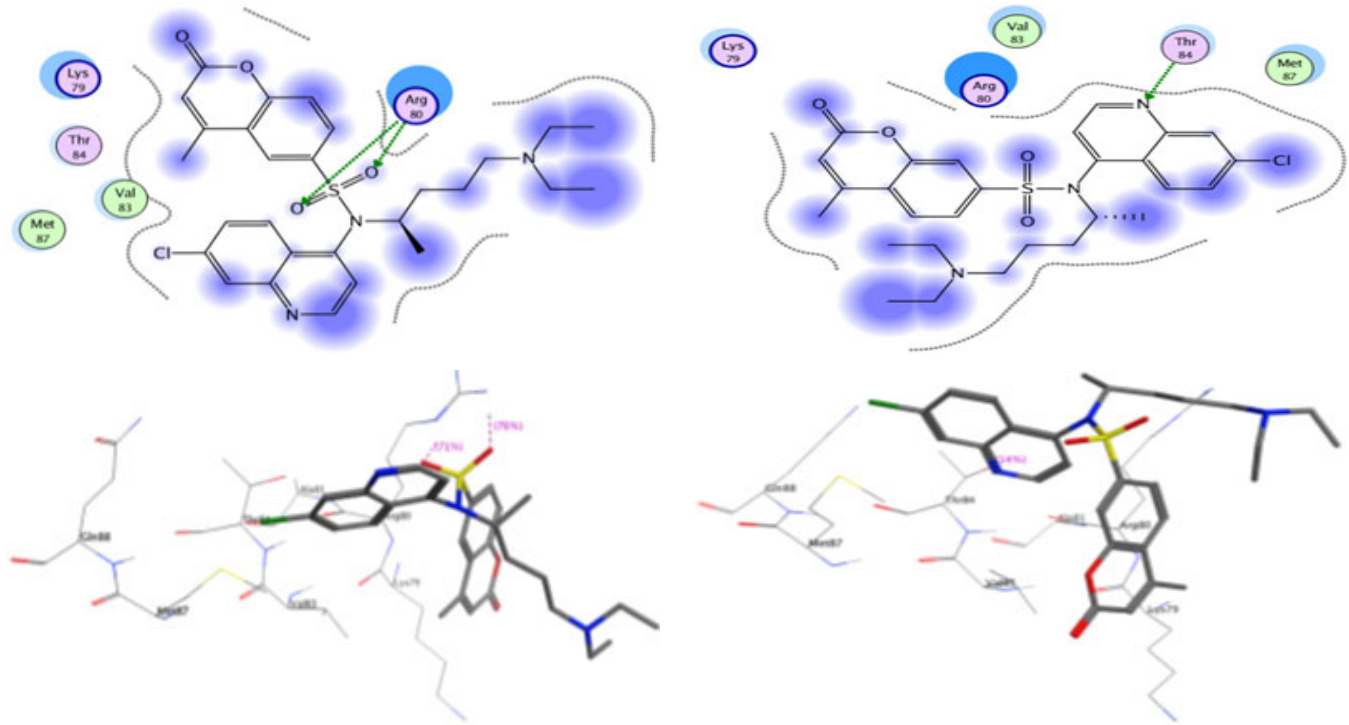


Fig. 4. Energy gap and electrophilicity for all compounds using HF/6-31G method



Structure **4**-More stable with 6YI3 Structure **3**-Less stable with 6YI3

Fig. 5. Molecular docking between the compounds **3** and **4** with 6YI3 protein



Structure **4**-More stable with 6YHU Structure **3**-Less stable with 6YHU

Fig. 6. Molecular docking between the compounds **3** and **4** with 6YHU protein

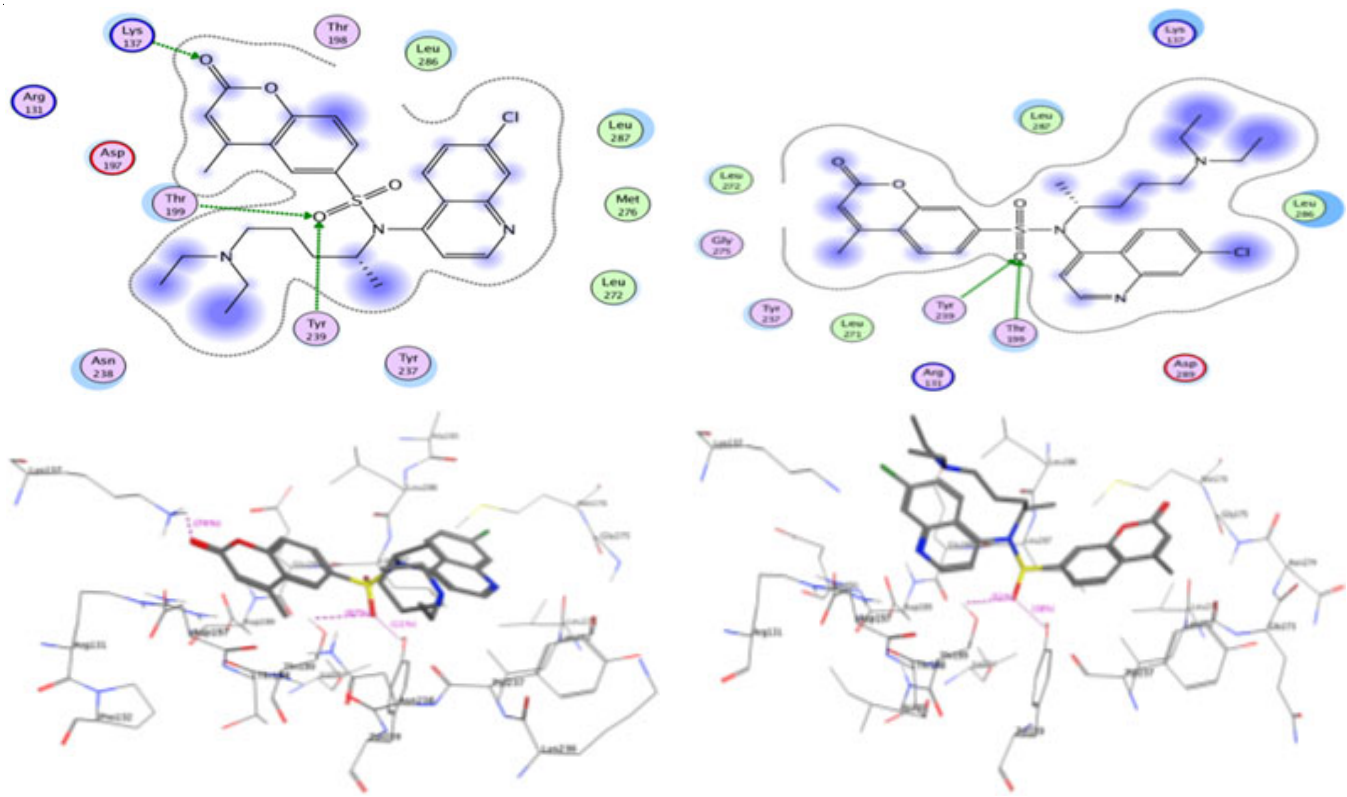


Fig. 7. Molecular docking between the the compounds **3** and **4** with 6LU7 protein

TABLE-4
DOCKING BETWEEN THE TWO STRUCTURES WITH PROTEIN

Structure	S	E_conf	E_place	E_score1	Protein
4	-13.1961	1.644563	-31.28	-13.1961	6LU7
3	-9.14564	1.631138	-52.3048	-9.14564	
4	-8.45929	3.000169	-30.98	-8.45929	6YHU
3	-6.94332	1.411965	-29.3736	-6.94332	
4	-10.4457	2.114064	-22.1666	-10.4457	6YI3
3	-8.05313	2.890073	-53.2142	-8.05313	

as inhibitors for COVID-19 by DFT and molecular docking calculations. The compounds were investigated using quantum calculations by employing the basis set (HF/6-31G and HF/STO-3G) and AM1 methods. The physical properties of the final and initial predicted mechanisms in the gaseous phase and according to electrophilicity, the reactivity of compound **3** was higher than that of compound **4**. Moreover, ΔG values and steric energies further support the selection of compound **4**.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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