

In-Silico Investigation on Chloroquine Derivatives: A Potential Anti-COVID-19 Main Protease

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Abstract: SARS-CoV-2 (Covid 19) continues to be a great threat to lives globally as it causes illnesses such as the common cold, severe acute respiratory syndrome and spreads easily among people. In this work, thirteen molecular compounds were studied via quantum chemical calculations, molecular docking, and dynamic simulation, and ADMET (absorption, distribution, metabolism, excretion, and toxicity). The obtained descriptors (Log P, HBA, HBD, and molecular weight) showed that the studied compounds have the ability to act as a drug. Thus, it was detected that all the studied selected compounds possess a better tendency to inhibit main coronavirus protease; however, compound C₁ has a higher tendency to inhibit main coronavirus protease than the other compounds, including the standard (Chloroquine). ADMET properties of compound C₁ proved that the predicted ADMET level was better than the ADMET properties of the referenced drug.

Keywords: chloroquine; COVID-19; SARS-CoV-2; molecular dynamic simulation; DFT; docking; ADMET.

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1. Introduction

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) or COVID-19 is a highly contagious disease that causes respiratory, gastrointestinal, and neurological diseases. The virus first appeared in December 2019, when a number of patients with pneumonia of unknown cause were noticed in Wuhan, China [1].

Due to the absence of any known cure and because of the situation of a “public health emergency”, many drugs have been tried lately in the treatment for COVID-19 that includes low-cost antimalarial drug chloroquine and its derivative hydroxychloroquine (HCQ), along with many other antiviral drugs such as Remdesivir, Ivermectin, and Nitazoxanide among others [2].

Chloroquine has a quinoline ring like quinine and a side chain identical to quinacrine; the chloride atom in the seventh position appears to be crucial to its antimalarial activity [3].

Since then, CQ and HCQ have been tested against Zika, Ebola, human immunodeficiency virus, hepatitis C virus, coronaviruses, and others [4], exhibiting broad-spectrum antiviral properties.

Presently there is no known specific, effective, proven pharmacological treatment for SARS-CoV-2. *In-vitro* studies have suggested that chloroquine, an immunomodulant drug traditionally used to treat malaria, effectively reduces viral replication in other infections, including the SARS-associated coronavirus (CoV) MERS-CoV [5,6].

In this work, fourteen molecular compounds were studied to identify the descriptors that predict the anti- SARS-CoV-2 activities of chloroquine derivatives using DFT and to study the physicochemical properties and pharmacokinetic properties using ADMETSAR and observe the molecular interactions between derivatives of chloroquine and COVID-19 main protease (PDB code: 6w63) [7] using *in silico* approaches.

2. Materials and Methods

2.1. Optimization.

Thirteen derivatives of Chloroquine including Chloroquine were optimized via *in silico* method using Spartan 14 software [8]. The molecular descriptors which includes molecular weight, hydrophobicity (Log P), volume (V), Area, polar surface area (PSA), ovality, dipole moment (DM), Hydrogen bond donor(HBA),Hydrogen bond acceptor (HBA) Highest occupied molecular Orbital (E_{HOMO}), Lowest unoccupied molecular orbital (E_{LUMO}) and Band gap ($E_{HOMO}-E_{LUMO}$) energies were studied to predict the antiviral activities of the compounds on Covid-19. The name of the studied compounds were ((4-((7-chloroquinolin-4-yl)amino)pentyl)(ethyl)amino)methanol (C₁), N4-(7-chloroquinolin-4-yl)-N1-ethyl-N1-(4-fluorobenzyl)pentane-1,4-diamine (C₂), N4-(7-chloroquinolin-4-yl)-N1-ethyl-N1-(fluoromethyl)pentane-1,4-diamine (C₃), N4-(7-chloroquinolin-4-yl)-N1-ethyl-N1-(2,2,2-trifluoroethyl)pentane-1,4-diamine (C₄), N4-(7-chloroquinolin-4-yl)-N1-methyl-N1-((trifluoromethoxy)methyl)pentane-1,4-diamine (C₅), N4-(7-chloroquinolin-4-yl)-N1-methyl-N1-(phenoxymethyl)pentane-1,4-diamine (C₆), N4-(7-chloroquinolin-4-yl)-N1-ethyl-N1-methylpentane-1,4-diamine (C₇), N4-(7-chloroquinolin-4-yl)-N1-(methoxymethyl)-N1-methylpentane-1,4-diamine (C₈), N4-(7-chloroquinolin-4-yl)-N1-methyl-N1-propylpentane-1,4-diamine (C₉), 2-((4-((7-chloroquinolin-4-yl)amino)pentyl)(methyl)amino)acetonitrile (C₁₀), N1-butyl-N4-(7-chloroquinolin-4-yl)-N1-methylpentane-1,4-diamine (C₁₁), N4-(7-chloroquinolin-4-yl)-N1-(furan-2-ylmethyl)-N1-methylpentane-1,4-diamine (C₁₂), N4-(7-chloroquinolin-4-yl)-N1-methyl-N1-(thiophen-2-ylmethyl)pentane-1,4-diamine (C₁₃), N1-((1H-pyrrol-2-yl)methyl)-N4-(7-chloroquinolin-4-yl)-N1-methylpentane-1,4-diamine (C₁₄) (Table 1).

2.2. Docking study.

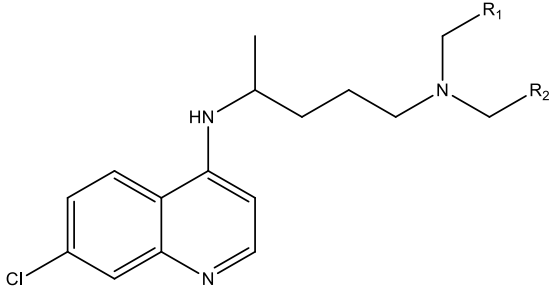
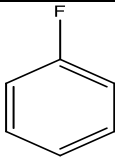
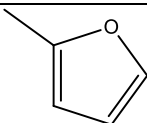
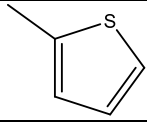
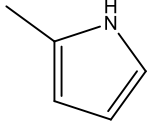
The docking study was executed by preparing the receptor (COVID-19 main protease with PDB code: 6w63) obtained from the protein data bank (www.rcsb.org) and chloroquine derivatives. Series of software were involved in accomplishing molecular docking to determine the ligand's affinity towards the target and to view the non-bonding interaction between the studied complexes. The software used were PyMOL, Autodock tool 1.5.6, autodock vina, and

Discovery studio. The observed grid box was: center (X = -26.479, Y = 12.595, Z = 58.704) and size (X = 54, Y = 68, Z = 72); and the spacing was set at 1.00Å.

2.3. ADMET properties.

ADMET SAR1, as an online ADMET software, was used to achieve absorption, distribution, metabolism, excretion, and toxicity (ADMET) of the studied compounds as well as the referenced drug (Chloroquine) [9]. Twenty-three factors were observed, and this includes Blood-Brain Barrier, Human Intestinal Absorption, Caco-2 Permeability, P-glycoprotein Substrate, P-glycoprotein Inhibitor, Renal Organic Cation Transporter, Subcellular localization, CYP450 2C9 Substrate, CYP Inhibitory Promiscuity, AMES Toxicity, Carcinogens, and Biodegradation.

Table 1. The schematic structures of the studied molecules.

		
	R₁	R₂
C ₁	OH	CH ₃
C ₂		CH ₃
C ₃	F	CH ₃
C ₄	CF ₃	CH ₃
C ₅	OCF ₃	H
C ₆	OC ₆ H ₅	H
C ₇	CH ₃	H
C ₈	OCH ₃	H
C ₉	OC ₂ H ₅	H
C ₁₀	CN	H
C ₁₁	C ₃ H ₇	H
C ₁₂		H
C ₁₃		H
C ₁₄		H

3. Results and Discussion

3.1. Calculated molecular properties from studied compounds.

Series of descriptors that describe potential anti- COVID-19 main protease activities of the studied derivatives of chloroquine were molecular weight (MW), hydrophobicity (Log P),

Hydrogen bond donor (HBA), Hydrogen bond acceptor (HBA), highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital (E_{LUMO}) and Bandgap ($E_{\text{HOMO}} - E_{\text{LUMO}}$) energies as presented in Table 2. The ability of the studied compounds to act as the drug-like compound was examined by considering the Lipinski rule of five ($\text{MW} \leq 500$ amu, $\text{Log P} \leq 5$, $\text{HBD} \leq 5$, $\text{HBA} \leq 10$), and it was observed that the calculated molecular weight, lipophilicity (Log P) hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) values were within the acceptable range; thus, the studied derivatives of chloroquine possess the ability to act as a drug. Other calculated descriptors were reported in Table 2.

Table 2. Calculated molecular descriptors for the studied compounds.

	HOMO (eV)	LUMO (eV)	BG	HBA	HBD	MW (amu)	Log p
C ₁	-5.47	-1.25	4.22	3	1	413.968	2.49
C ₂	-4.29	-1.72	2.57	3	1	337.87	0.51
C ₃	-5.65	-1.25	4.4	3	1	387.877	1.57
C ₄	-5.65	-1.25	4.4	4	1	403.876	0.00
C ₅	-5.46	-1.26	4.2	4	1	411.977	1.98
C ₆	-5.51	-1.25	4.26	3	1	333.907	1.14
C ₇	-5.47	-1.26	4.21	4	1	349.906	0.16
C ₈	-5.47	-1.25	4.22	3	1	361.961	1.89
C ₉	-5.69	-1.26	4.41	4	1	344.89	0.69
C ₁₀	-5.50	-1.25	4.25	3	1	347.934	1.56
C ₁₁	-5.41	-1.42	3.99	4	1	385.939	0.3
C ₁₂	-5.59	-1.24	4.35	4	1	402.006	1.02
C ₁₃	-5.41	-1.24	4.17	4	2	384.955	0.08
C ₁₄	-5.50	-1.25	4.25	4	2	335.879	-0.2

3.2. Docking studies on chloroquine derivatives and COVID-19 main protease.

The studied compounds were docked against COVID-19 main protease (PDB code: 6w63) to examine the binding affinity and non-bonding interaction present in the studied complexes. The calculated binding affinity for the studied complexes were -6.66 kcal/mol for C₁, -5.8 kcal/mol for C₂, -6.2 kcal/mol for C₃, -6.4 kcal/mol for C₄, -6.0 kcal/mol for C₅, -5.9 kcal/mol for C₆, -6.1 kcal/mol for C₇, -6.1 kcal/mol for C₈, -6.0 kcal/mol for C₉, -5.8 kcal/mol for C₁₀, -6.3 kcal/mol for C₁₁, -6.1 kcal/mol for C₁₂, and -6.3 kcal/mol for C₁₃. The docked compounds have nine (9) conformations each, and the conformation with the lowest binding affinity value is considered to be the best [10-25]; therefore, compound C₁ with -6.66 kcal/mol is considered to have the best ability to inhibit COVID-19 main protease than other studied compounds and the referenced drug. This revealed that the derivative ($R_1 = \text{OH}$ and $R_2 = \text{CH}_3$) attached to the studied parent compound enhanced the biological activity of the studied parent compound than other studied derivatives.

The residue involved in each interaction were Cys 44, MET 49, MET 165, CYS 145, HIS 163 for C₁; MET 49, HIS 41, HIS 164, CYS 44, CYS 145, MET 165, GLN 189, ARG 188 for C₂; CYS 44, CYS 145, MET 49, HIS 41, GLU 145 for C₃; GLU A:166, ARG A:188, THR A:190, GLN A:192 for C₄; CYS 145, GLU 166 for C₅; CYS 44, CYS 145, HIS 41, HIS 164, MET 165, MET 49, PRO 52 for C₆; MET 49, CYS 44, HIS 41, MET 165, HIS 164, GLU 166, GLN 192 for C₇; CYS 145, HIS 41, CYS 44, MET 49, PRO 168, GLU 166, LEU 167 for C₈; CYS 44, PRO 52, CYS 145, MET 49, HIS 41, MET 165, HIS 164, GLN 189 for C₉; CYS 44, MET 165, HIS 41, HIS 164, PRO 168, LEU 167, CYS 145 for C₁₀; CYS 145, MET 165, HIS 41 for C₁₁; CYS 44, PRO 52, HIS 41, MET 49, HIS 164, CYS 145, MET 165 for C₁₂; CYS 44, MET 165, PRO 168, HIS 41, CYS 145 for C₁₃ (Table 3) (Figure 1).

Table 3. Binding affinity and interactions among residues of drugs and COVID-19 main protease.

S. No	Binding affinity kcal/mol	Amino acid residue
C ₁	-6.6	CYS A:44, MET A:49, MET A:165, CYS A:145, HIS A:163
C ₂	-5.8	MET A:49, HIS A:41, HIS A:164, CYS A:44, CYS A:145, MET A:165, GLN A:189, ARG A:188
C ₃	-6.2	CYS A:44, CYS A:145, MET A:49, HIS A:41, GLU A:145
C ₄	-6.4	GLU A:166, ARG A:188, THR A:190, GLN A:192
C ₅	-6.0	CYS A:145, GLU A:166
C ₆	-5.9	CYS A:44, CYS A:145, HIS A:41, HIS A:164, MET A :165, MET A:49, PRO A:52
C ₇	-6.1	MET A:49, CYS A:44, HIS A:41, MET A :165, HIS A :164, GLU A:166, GLN A:192
C ₈	-6.1	CYS A :145, HIS A:41, CYS A:44, MET A:49, PRO A:168, GLU A:166, LEU A:167
C ₉	-6.0	CYS A:44,PRO A:52, CYS A:145, MET A:49, HIS A:41, MET A:165, HIS A:164, GLN A:189
C ₁₀	-5.8	CYS A:44, MET A:165,HIS A:41, HIS A:164, PRO A:168, LEU A:167,CYS A:145
C ₁₁	-6.3	CYS A:145, MET A:165, HIS A :41
C ₁₂	-6.1	CYS A:44, PRO A:52, HIS A:41, MET A:49, HIS A:164, CYS A:145, MET A:165
C ₁₃	-6.3	CYS A:44, MET A:165, PRO A:168, HIS A:41, CYS A145
Chloroquine	-6.1	HIS A:41, CYS A:145, MET A:49, CYS A:44, ARG A:188, THR A:190, GLN A:192, GLU A:166

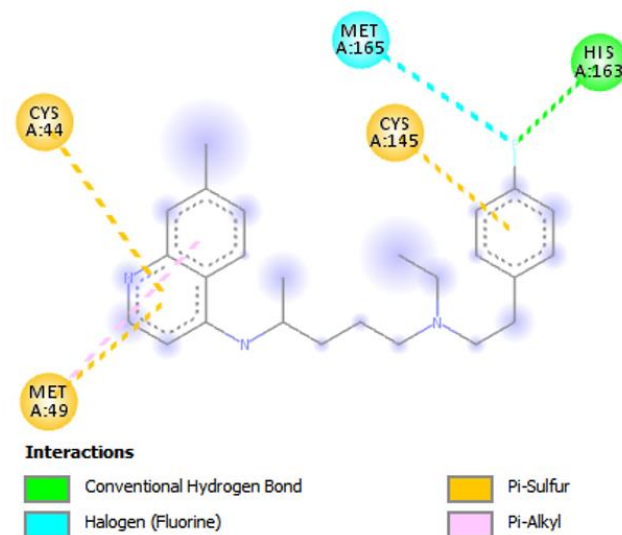


Figure 1. 2D structures of COVID-19 main protease (PDB code: 6w63) and compound C₁.

3.3. Molecular dynamics simulation study.

3.3.1. Root mean square deviation analysis.

The values of the calculated root mean square deviation (RMSD) of the backbone atoms of the studied receptor were used to determine the degree of deviation from the initial structure when binding and the stability of the complexes during the 50,000ps (50 ns) MD simulation time. The RMSD of the studied complex shows a stable conformation, particularly in the last 10 ns of the simulation, which indicated stable conformation for the studied systems, as shown in Figure 2. The calculated average RMSD values are 0.15 Å° for C₁ and 0.25 for Chloroquine.

3.3.2. Root of mean square fluctuation.

The studied root means square fluctuation (RMSF) helps determine the flexibility of residues upon binding of the two compounds tested during (50 ns) simulation time, as shown in Figure 3. It is noticeable that there is a similarity in the trend at which the observed residue

oscillated; though, little variation was detected between the two compounds. As shown in Figure 3, it was established that compound C₁ displayed a minor degree of deviation, and this demonstrates a higher level of affinity for it to inhibit main coronavirus protease than chloroquine.

3.3.3. Binding free energy.

As revealed in Table 4 below, the calculated binding energy proved that compound C₁ possesses a better ability to inhibit COVID-19 main protease (PDB code: 6w63) than the standard. The calculated free energy for C₁ includes van der Waal energy (-190.113 kJ/mol), electrostatic energy (-13.126 kJ/mol), polar solvation energy (105.195 kJ/mol) and (-20.887 kJ/mol) while the values for Chloroquine are -171.754 kJ/mol, -6.654 kJ/mol, 64.576 kJ/mol and -18.386 kJ/mol respectively. This shows that van der Waal energy, polar solvation energy, electrostatic solvation energy, and SASA energy favored the binding of compound C₁ to main coronavirus protease.

3.3.4. Solvent Accessible Surface Area (SASA).

Solvent accessible surface area (SASA) analysis was used to determine the interaction between complexes and solvents [26]. In Figure 4, it was observed that the SASA values for the protein-ligand complexes during MD were relatively stable; this showed that there were no significant changes in the protein structure. Also, compound C₁ has a higher SASA value, which means C₁ should interact more and be accessible for solvents (Figure 4).

3.3.5. Radius of Gyration (Rg) in MD simulation.

The radius of gyration (Rg) was used to discover the compactness changes of the ligand-protein complex during the 50,000ps (50 ns) MD simulation time. No significant changes were observed for C₁ and Chloroquine, which implied great stability and compactness of the complexes. Although, a little deviation was noticed for chloroquine around 15000ps and 25000ps, which suggested a loss of compactness for its complex (Figure 5).

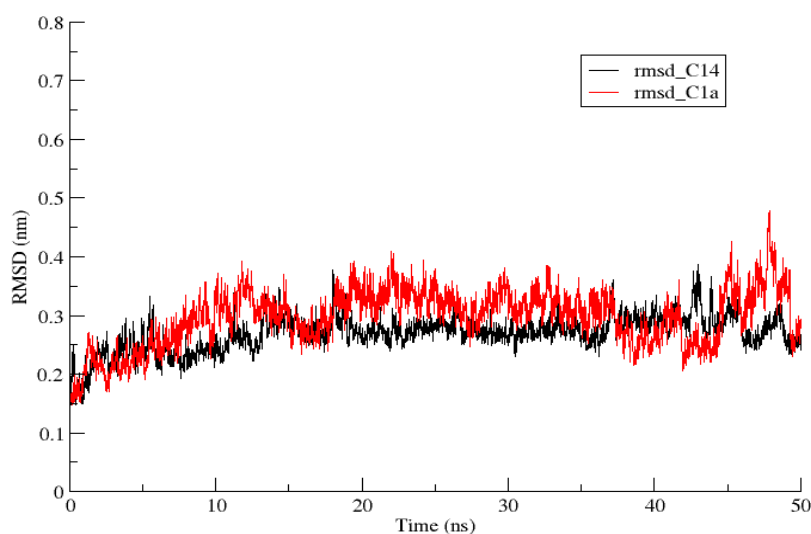


Figure 2. Root mean square deviation of the studied complexes.

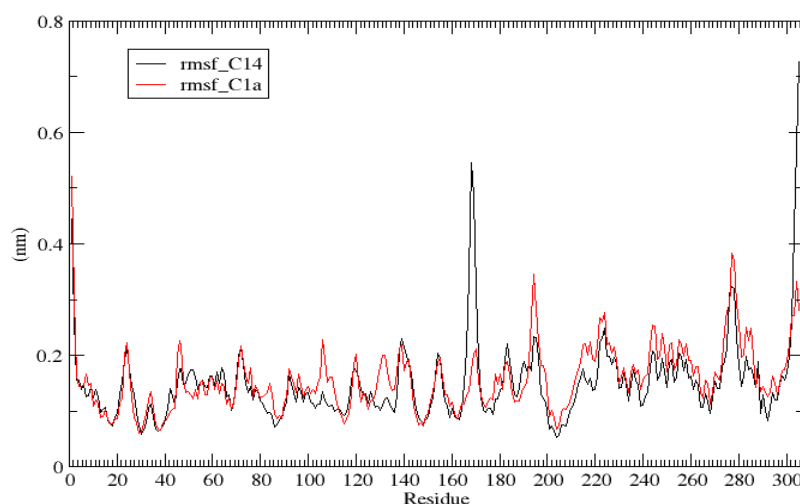


Figure 3. Root mean square fluctuation of the studied complexes.

Table 4. Calculated binding free energies for compound C₁ and reference drug.

	Van der Waal energy (kJ/mol)	Electrostatic energy (kJ/mol)	Polar solvation energy (kJ/mol)	SASA energy (kJ/mol)	Binding energy (kJ/mol)
Rd	-171.754 ± 0.698	-6.654 ± 0.204	64.576 ± 0.422	-18.386 ± 0.059	-132.202 ± 0.712
C1	-190.113 ± 0.622	-13.126 ± 0.423	105.195 ± 0.806	-20.887 ± 0.068	-118.924 ± 0.693

Note: Rd: Reference drug; C1: ((4-((7-chloroquinolin-4-yl)amino)pentyl)(ethyl)amino)methanol

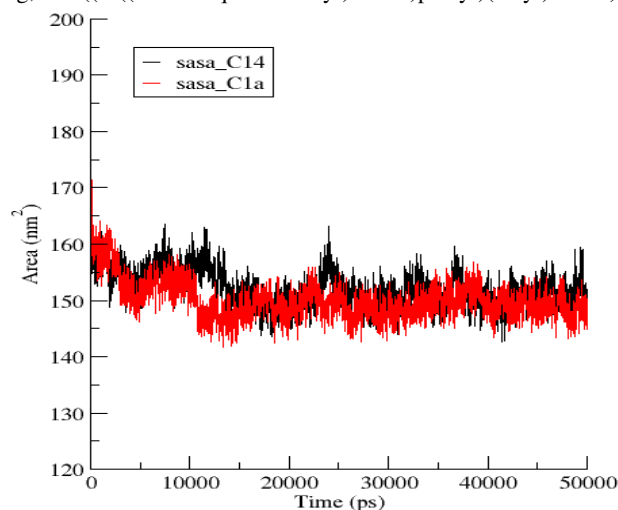


Figure 4. Solvent accessible surface area of the studied complexes.

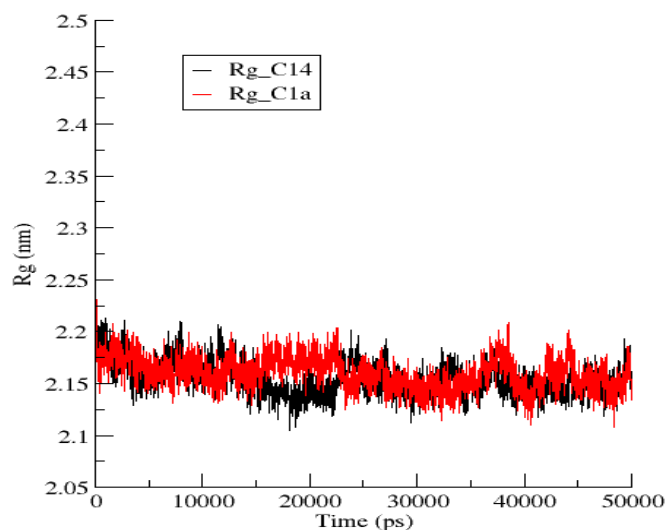


Figure 5. Radius of gyration of the studied complexes.

3.4. ADMET properties of studied selected compounds.

The selected compounds were subjected to an ADMET study using the admetSAR server to predict the pharmacokinetic properties. A higher value of HIA denotes that the compound could be better absorbed from the intestinal tract upon oral administration [27]; thus, it was observed that the calculated human intestinal absorption (HIA) value for compound C₁ was closer to the calculated value for Chloroquine (Standard). More so, the calculated blood-brain barrier (BBB) value, which reveals the penetration level of drug-like compound, showed that the value calculated for compound C₁ was higher than that of the reference drug, which revealed its efficiency level. Other considered ADMET factors were within the same range as the studied referenced drug [28] (Table 5).

Table 5. Predicted ADMET properties of compound C₁ and Chloroquine.

Mode	Compound C ₁		Chloroquine	
	Result	Probability	Result	Probability
Blood-Brain Barrier	BBB+	0.8121	BBB+	0.5355
Human Intestinal Absorption	HIA+	0.9974	HIA+	0.9881
Caco-2 Permeability	Caco2+	0.5717	Caco2-	0.5199
P-glycoprotein Substrate	Substrate	0.8065	Substrate	0.8303
P-glycoprotein Inhibitor	Inhibitor	0.6577	Non-inhibitor	0.6523
	Inhibitor	0.6432	Inhibitor	0.6471
Renal Organic Cation Transporter	Inhibitor	0.6278	Non-inhibitor	0.6248
Subcellular localization	Lysosome	0.9085	Lysosome	0.7498
CYP450 2C9 Substrate	Non-substrate	0.8525	Non-substrate	0.8141
CYP450 2D6 Substrate	Substrate	0.7969	Non-substrate	0.8754
CYP450 3A4 Substrate	Substrate	0.552	Non-substrate	0.5000
CYP450 1A2 Inhibitor	Non-inhibitor	0.7441	Non-inhibitor	0.6459
CYP450 2C9 Inhibitor	Non-inhibitor	0.8682	Non-inhibitor	0.8562
CYP450 2D6 Inhibitor	Non-inhibitor	0.8664	Non-inhibitor	0.6726
CYP450 2C19 Inhibitor	Non-inhibitor	0.8331	Non-inhibitor	0.8903
CYP450 3A4 Inhibitor	Non-inhibitor	0.7046	Non-inhibitor	0.7419
CYP Inhibitory Promiscuity	High CYP Inhibitory Promiscuity	0.5	Low CYP Inhibitory Promiscuity	0.7470
Human Ether-a-go-go-Related Gene Inhibition	Weak inhibitor	0.7287	Weak inhibitor	0.6601
	Inhibitor	0.8433	Inhibitor	0.7440
AMES Toxicity	AMES toxic	0.8733	AMES toxic	0.6936
Carcinogens	Non-carcinogens	0.8529	Non-carcinogens	0.8100
Fish Toxicity	High FHMT	0.9895	High FHMT	0.9494
Tetrahymena Pyriformis Toxicity	High TPT	0.9981	High TPT	0.9940
Honey Bee Toxicity	Low HBT	0.8748	Low HBT	0.8661
Biodegradation	Not ready biodegradable	1.0000	Not ready biodegradable	1.0000

4. Conclusions

In this work, thirteen chloroquine derivatives were examined using the density functional theory method for optimization, docking, and molecular dynamics simulation studies to detect the biological interaction between the selected compounds and coronavirus main protease. It was observed that the studied compounds proved to be active potentials, anti-COVID-19 main protease agents. Also, compound C₁ possesses better potentials to inhibit COVID-19 main protease than other studied compounds and the standard. Moreover, the calculated actual binding energy for compound C₁ using molecular dynamic simulation methods further confirmed its ability to inhibit main coronavirus protease than other studied compounds, including the standard (Chloroquine).

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Conflicts of Interest

The authors declare no conflict of interest.

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