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Original article

DFT and molecular docking study of chloroquine derivatives as antiviral to coronavirus COVID-19

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The recently emerged COVID-19 virus caused hundreds of thousands of deaths and instigated a widespread fear, threatening the world’s most advanced health security. In 2020, chloroquine derivatives are among the drugs tested against the coronavirus pandemic and showed an apparent efficacy. In the present work, the chloroquine and the chloroquine phosphate molecules have been proposed as potential antiviral for the treatment of COVID-19 diseases combining DFT and molecular docking calculations. Molecular geometries, electronic properties and molecular electrostatic potential were investigated using density functional theory (DFT) at the B3LYP/6-31G* method. As results, we found a good agreement between the theoretical and the experimental geometrical parameters (bond lengths and bond angles). The frontier orbitals analysis has been calculated at the same level of theory to determine the charge transfer within the molecule. In order to perform a better description of the FMOs, the density of states was calculated to provide information on the chemical reactivity of molecule and also to describe the intermolecular interactions. All these studies help us a lot in determining the reactivity of the mentioned compounds. Finally, docking calculations were carried out to determine the pharmaceutical activities of the chloroquine derivatives against coronavirus diseases. The choice of these ligands was based on their antiviral activities.

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1. Introduction

In late December 2019, the coronavirus (Covid and R Team, 2019) was first reported in humans in Wuhan, China, and appeared as a rapidly spreading pandemic (Wang et al., 2020; Dong et al., 2020). About 46 million people worldwide have been infected as of 1, November 2020, and over 1 197 000 have died. It is worthy to mention that this pandemic has the same symptoms as a flu. Fatigue, fever, headache, runny nose and dry cough are the principal clinical symptoms of COVID-19. Thus far, there is no effective antiviral medication or vaccine against COVID-19 virus has been developed. Where the World Health Organization announced it as one of the most dangerous health catastrophes in human history (Bheenaveni, 2020) since this virus is accelerating very quickly more than predicted by experts (Al Shamsi et al., 2019). Therefore, searching for effective antiviral agents to battle against this virus is urgently needed. In this context, our investigations are destined for the development of therapeutic agents for COVID-19 diseases. Many scientists are working on the designing of efficacious antiviral agents with few aspect effects. Where recent research informed an inhibitor effect of the chloroquine and its derivatives on the growth of coronavirus (Gautret et al., 2020; Romano et al., 2020; Lecuit, 2020). Clinical trials have been done on Chinese patients COVID-19; have shown that the chloroquine has a great effect in terms of clinical results and viral clearance, in comparison to the control groups (Gautret et al., 2020). They have been proposed as a potential antiviral for the treatment of COVID-19 diseases based on their antiviral activities (Touret and X., 2020; Colson et al., 2020).

In this study, we evaluated the antiviral efficiency of two approved drugs which are chloroquine and chloroquine phosphate against the COVID-19 using molecular docking calculations. Docking is a technique of designing drug molecules via computer-aided by simulating the geometric of these molecules and their
intermolecular forces (Noureldine et al., 2020a, 2020b). From this calculation, we can predict the different interactions between medications and targets which have an important role in the investigation of the mechanism of the effects of drugs. In this context, many nowadays papers is dedicated to searching in drug design using molecular docking studies (Jomaa et al., 2020; Sagaama et al., 2020a, 2020b; Issaoui et al., 2017). In the same frame, we can cite our previous paper (Romani et al., 2020) in which we used molecular docking analysis in the determination of the biological activity of the Niclosamide compound. As a result, the niclosamide is found to be a good inhibitor of the COVID-19 virus and can, therefore, be effective in controlling this disease.

The main contribution of this paper is to identify the potency of inhibition of chloroquine derivatives against COVID-19 virus by using a molecular docking study. To this end, we first determine the optimized structures of chloroquine and chloroquine phosphate molecules by using the density functional theory (DFT) at B3LYP/6-31G* level of theory. Utilizing optimized structures is more exact in docking calculations, which makes the program more trustworthy to be employed in structure-based drug design. Subsequently, their reactivities were foreseen at the same level of theory by using the frontier orbital studies (Brédas, 2014; Parr and Pearson, 1983). From this analysis, we can found the most reactive antiviral ligand. Moreover, molecular electrostatic potentials surfaces were carried out to investigate which are the most reactive nucleophilic and electrophilic regions of a molecule against reactive biological potentials. Docking calculations were performed using four structures of COVID-19 (PDB codes: 6M03, 5R81, 6LU7) (http://www.rcsb.org/). Basing on the binding affinities and the different interactions that exist between amino acid residues and ligands, molecular docking results were discussed.

2. Computational details

2.1. DFT calculations

The GaussView program (GaussView, Guassian, Inc.) was utilized to model the initial structures of the chloroquine and the chloroquine phosphate molecules. Subsequently, their molecular geometries optimizations were carried out in the gas phase with the density functional theory (DFT) with the Gaussian 09 software package (Gaussian 09, Revision C.01, Frisch et al., 2009). All the quantum-chemical calculations have been performed via the hybrid B3LYP (Becke’s three parameter hybrid functional with Lee-Yang-Parr correlation functional LYP (Lee et al., 1988; Becke, 1993) at 6-31G* basis set. Furthermore, several electronic properties for instance the frontier molecular orbitals, gap energies, reactivity descriptors were computed using TD-DFT approach (Liu et al., 2015; Becke, 1993). The density of states (DOS) plots were obtained using Gauss-Sum software (O’Boyle et al., 2008).

2.2. Ligands and proteins preparation

The 3D structures of COVID-19 protein were retrieved from the RCSB PDB database (http://www.rcsb.org). The Protein Data Bank (PDB) archive contains thousand protein structures obtained either by crystallography X-ray or by NMR. Concerning ligands, the 2D structures of chloroquine and chloroquine phosphate were extracted from the PubChem online database (https://pubchem.ncbi.nlm.nih.gov/). The ligands were saved in the MOL file format. Then, they were converted to a PDB file format by using Accelrys Discovery Studio Visualizer (Visualizer, 2005). Thereafter, Rapid-Screening docking was carried out using iGEMDOCK program (Yang and Chen, 2004). It is a Drug Design System for docking calculations and screening by BioXGEM labs. All the trials were docked with a population size set to 800, with 80 generations and 10 solutions.

3. Results and discussion

3.1. Optimization of chloroquine and chloroquine phosphate

Optimized structures and numbering of atoms of chloroquine and chloroquine phosphate molecules are shown graphically in Figs. 1 and 2, obtained at B3LYP/6-31G* method. Table 1 illustrates their geometrical parameters such as the calculated total energies, the dipole moments, the RMS and the maximum Cartesian force. The global minimum energies are found to be $-1326.0352$ a.u ($\approx -36083$ eV) and $-2614.3242$ a.u ($\approx -71139$) for chloroquine and chloroquine phosphate, respectively. The RMS Cartesian force values are equal to 2.412 0.10 $\delta$ and 0.04067 in chloroquine and chloroquine phosphate. Their maximum Cartesian forces are found to be 8.593 0.10 $\delta$ and 0.1449. The dipole moment of a molecule is given in the form of a three-dimensional vector and which reflects the molecular charge distribution. Hence, it can be employed as a descriptor to describe the charge movement throughout the molecule. As a result of DFT/B3LYP/6-31G* calculations, the highest dipole moment was observed for the chloroquine phosphate ($-24.49$ Debye) whereas the smallest one was observed for the chloroquine ($-6.05$ Debye). Of course, the adding of other atoms in the geometry of the chloroquine has an influence on their stability. We can notice that the chloroquine compound becomes more stable when adding the phosphate groups since the global minimum energy decreases.

The optimized geometrical parameters of chloroquine derivatives have been determined by the above method and they are given in Tables 2 and 3 with the experimental bond angles and bond lengths. First, we observed that the theoretical bond lengths of chloroquine compound are almost similar with the experimental results (Busseta and Courseille, 1973), since the value of RMSD is very small (0.001 Å). The same applies to the bond angles which have an RMSD value equal to 0.298°. Some thing for the chloroquine phosphate, according to the result as collected in table 3 the bond distances and bond angles show good agreement with the experimental data (Albesa-Jové et al., 2008). We find that the RMSD value is equal to 0.065 Å for the bond distances and 3.382° for the bond angles. Results reveal that the carbon–carbon bond distances are found in the range 1.374–1.546 Å for C20–C22 and C5–C7, respectively for the chloroquine. In the benzene ring (I), the carbon–carbon bond lengths C12–C16, C12–C18, C17–C20, C18–C21, C20–C22 and C21–C22 are 1.345, 1.418, 1.421, 1.378, 1.374 and 1.411 Å, respectively. The C-C bond alienation in the pyridine ring (II) is between 1.394 Å (for C21–C16 bond) and 1.445 Å (for C12–C13 bond). While, for chloroquine phosphate, the bond length between two carbon–carbon in the two rings is in the range 1.383–1.419 Å for benzene and 1.366 to 1.464 Å for pyridine ring. It is seen that the B3LYP calculated hydrogen bonding distances C–H vary from 1.009 Å (for N2–H30) to 1.099 Å (for C5–H24) for chloroquine and from 1.084 Å (for C10–H27 bond) to 1.524 Å (for C21–C22 bond) for chloroquine phosphate. Three nitrogen N atoms exist in the structure of chloroquine: the order of the N–C bond length is N2–C10 > N2–C11 > N2–C8 > N3–C7 > N3–C2 > N4–C17 > N4–C19 having values 1.470 > 1.469 > 1.467 > 1.465 > 1.370 > 1.365 > 1.319 Å, respectively. The bond distance of N2–H30 is equal to 1.009 Å. The bond angle of chlorine of the C7–N3–H30 and C7–N2–H30 are ~ 115.047° and ~ 116.505°, respectively. Concerning the
chloroquine phosphate, we note that the single N₅-C₆ bond length of 1.387 Å for ring pyridine is higher than the N₅-C₄ double bond (1.353 Å). The P-O bond lengths are obtained to be in range 1.489–1.693 Å (for P₅₈-O₆₁ and P₅₈-O₆₂). The O-P-O bond angles are reported in range 107.7–112.02°, whereas it is computed in range 102.543–124.278°. The C₈-Cl bond length is observed at 1.743 Å and calculated at 1.748 Å. The C₉-C₈-Cl and C₈-C₉-C₁₀ bond angles are at 119.733° and 116.940°, respectively.

3.2. Frontier orbitals and quantum chemical calculations

Frontier molecular orbitals (FMOs) often play dominant roles in molecular systems. The fundamental idea of this theory can be abridged in the form of a simple rule telling the condition for a simple course of the reaction by the requirement of the maximal positive overlap between LUMO (empty state) and HOMO (filled state) orbitals. LUMO (lowest unoccupied molecular orbital) is directly related to electron affinity, while HOMO (highest occupied molecular orbital) is related to ionization potential (Xavier and Periandy, 2015; Abraham et al., 2017). These orbitals help to understand the chemical stability and the reactivity of the molecule (Asiri et al., 2011; Kosar, 2011). In order to predict the energetic behaviors and the reactivity of the chloroquine and the chloroquine phosphate against COVID-19 virus, the FMOs in the electronic transitions and their energies difference Eg are determined. A detailed analysis of the HOMOs and LUMOs orbitals is
Table 2
Calculated geometrical parameters for the chloroquine compound compared with the experimental ones by using B3LYP/6-31G* basis set.

| Parameters          | Experimental | Theoretical | Parameters          | Experimental | Theoretical |
|---------------------|--------------|-------------|---------------------|--------------|-------------|
| Bond lengths (Å)    |              |             |                     |              |             |
| Cl-C22              | 1.755        | 1.760       | Cl-C15-C16          | 1.393        | 1.394       |
| N2-C8               | 1.469        | 1.467       | C12-C17             | 1.432        | 1.432       |
| N2-C10              | 1.460        | 1.470       | C13-C18             | 1.418        | 1.418       |
| N2-C11              | 1.498        | 1.469       | C14-H33             | 1.095        | 1.095       |
| N2-C12              | 1.500        | 1.465       | C14-H30             | 1.096        | 1.096       |
| N2-C13              | 1.371        | 1.370       | C14-H40             | 1.096        | 1.096       |
| N2-H34              | 1.009        | 1.009       | C15-H41             | 1.095        | 1.095       |
| N4-C17              | 1.344        | 1.365       | C16-H42             | 1.096        | 1.096       |
| N4-C19              | 1.368        | 1.320       | C16-H43             | 1.096        | 1.096       |
| C5-C6               | 1.534        | 1.534       | C17-C20             | 1.407        | 1.407       |
| C5-C7               | 1.546        | 1.546       | C17-C23             | 1.403        | 1.403       |
| C5-H23              | 1.098        | 1.098       | C17-H20             | 1.421        | 1.421       |
| C6-C8               | 1.100        | 1.100       | C18-C21             | 1.407        | 1.407       |
| C6-C9               | 1.108        | 1.108       |                      |              |             |
| RMSD                | 0.001 Å      |             |                     |              |             |
| Bond angles (°)     |              |             |                     |              |             |
| C8-N2-C10           | 112.84       | 112.103     | Cl-C15-C16          | 110.29       | 109.196     |
| C8-N2-C11           | 112.23       | 112.200     | H30-C17-C18         | 110.89       | 109.039     |
| C8-N2-C13           | 111.78       | 111.972     | N2-C15-C16          | 120.83       | 120.095     |
| C8-N2-C12           | 124.77       | 125.707     | N2-C15-C10          | 124.34       | 123.092     |
| C7-N3-C12           | 115.049      | 116.048     | Cl-C17-C18          | 116.79       | 116.790     |
| C7-N3-C10           | 116.50       | 116.505     | Cl-C17-C18          | 117.68       | 117.797     |
| C7-N3-C14           | 116.07       | 116.079     | Cl-C17-C18          | 124.08       | 123.818     |
| C5-C6-C8            | 112.5(4)     | 112.597     | H30-C14-C19         | 108.5(3)     | 108.529     |
| C5-C6-H25           | 109.59       | 109.519     | H30-C14-C19         | 108.5(3)     | 108.529     |
| C5-C7-C9            | 113.83       | 113.289     | H30-C14-C19         | 118.952      | 118.959     |
| C5-C7-H27           | 110.24       | 110.944     | H30-C14-C19         | 118.952      | 118.959     |
| C5-C7-H30           | 109.78       | 109.513     | H30-C14-C19         | 118.952      | 118.959     |
| C5-C7-H33           | 109.59       | 109.436     | H30-C14-C19         | 118.952      | 118.959     |
| C5-C7-H31           | 106.122      | 106.122     | N2-C6-C20           | 119.7354     | 119.736     |
| C5-C7-H32           | 110.24       | 110.944     | Cl-C17-C20          | 119.17       | 119.139     |
| C5-C7-H33           | 108.78       | 108.140     | Cl-C17-C20          | 119.17       | 119.139     |
| C5-C7-H34           | 109.59       | 109.436     | N2-C6-C20           | 119.17       | 119.139     |
| C5-C7-H35           | 106.122      | 106.122     | N2-C6-C20           | 119.17       | 119.139     |
| C5-C7-H36           | 110.24       | 110.944     | Cl-C17-C20          | 119.17       | 119.139     |
| C5-C7-H37           | 108.78       | 108.140     | Cl-C17-C20          | 119.17       | 119.139     |
| C5-C7-H38           | 109.59       | 109.436     | N2-C6-C20           | 119.17       | 119.139     |
| C5-C7-H33           | 106.122      | 106.122     | N2-C6-C20           | 119.17       | 119.139     |
| Cl-C22              | 110.7       | 110.7       | Cl-C15-C16          | 110.7       | 110.7       |
| Cl-C22              | 110.7       | 110.7       | Cl-C15-C16          | 110.7       | 110.7       |
| Parameters | Chloroquine phosphate | Calculated and observed geometrical parameters for the chloroquine phosphate. |
|-----------|-----------------------|--------------------------------------------------------------------------|
| Bond lengths (Å) | | |
| N1-C2 | 1.409(2) | C2-N18 | 1.5069(6) |
| N1-C13 | 1.4967(9) | C17-H36 | 0.9994 |
| N1-H48 | 1.0018 | C17-H37 | 1.0005 |
| N1-C13 | 1.4967(9) | N18-C21 | 1.5083(6) |
| N1-H48 | 1.0018 | N18-H50 | 0.9995 |
| C2-C3 | 1.415(3) | C2-C4 | 1.40(3) |
| C2-C3 | 1.415(3) | C2-H37 | 1.0000 |
| C3-C4 | 1.400(3) | C3-H36 | 1.0000 |
| C3-C4 | 1.400(3) | C3-H37 | 1.0000 |
| N1-C13 | 1.4967(9) | C3-H38 | 1.0010 |
| N1-H48 | 1.0018 | C3-H39 | 1.0010 |
| C2-C3 | 1.415(3) | C4-N5 | 1.386(1) |
| C2-C3 | 1.415(3) | C4-H24 | 0.999 |
| C3-C4 | 1.400(3) | C4-H24 | 0.999 |
| C3-C4 | 1.400(3) | N5-C6 | 1.382(3) |
| C3-C4 | 1.400(3) | N5-H49 | 0.998 |
| C6-C7 | 1.403(1) | C6-C11 | 1.417(3) |
| C6-C7 | 1.403(1) | C6-H25 | 0.997 |
| C7-C8 | 1.411(3) | C7-C9 | 1.396(3) |
| C7-C8 | 1.411(3) | C7-H26 | 0.999 |
| C8-C9 | 1.396(3) | C8-Cl | 1.743(3) |
| C8-C9 | 1.396(3) | C8-H27 | 1.0000 |
| C9-C10 | 1.373(1) | C9-H28 | 1.0000 |
| C9-C10 | 1.373(1) | C9-H28 | 1.0000 |
| C10-C11 | 1.431(3) | C10-H29 | 1.0010 |
| C10-C11 | 1.431(3) | C10-H29 | 1.0010 |
| C13-C14 | 1.5142(6) | C13-C15 | 1.5417/7(7) |
| C13-C14 | 1.5142(6) | C13-C15 | 1.5417/7(7) |
| C13-C14 | 1.5142(6) | C13-C15 | 1.5417/7(7) |
| C16-C17 | 1.5100(5) | C16-C17 | 1.5100(5) |
| C16-C17 | 1.5100(5) | C16-C17 | 1.5100(5) |
| C16-C17 | 1.5100(5) | C16-C17 | 1.5100(5) |
| RMSD | 0.065 Å | | |

Bond angles (°)

| Parameters | Chloroquine phosphate | Calculated and observed geometrical parameters for the chloroquine phosphate. |
|-----------|-----------------------|--------------------------------------------------------------------------|
| C2-N1-C13 | 121.5(1) | C2-N1-C13 | 121.5(1) |
| C2-N1-C13 | 121.5(1) | C2-N1-C13 | 121.5(1) |
| C2-N1-C13 | 121.5(1) | C2-N1-C13 | 121.5(1) |
| C2-N1-C13 | 121.5(1) | C2-N1-C13 | 121.5(1) |
| N1-C2-C3 | 119.25 | N1-C2-C3 | 119.25 |
| N1-C2-C3 | 119.25 | N1-C2-C3 | 119.25 |
| N1-C2-C3 | 119.25 | N1-C2-C3 | 119.25 |
| N1-C2-C3 | 119.25 | N1-C2-C3 | 119.25 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |
| N1-C13-C14 | 120.7 | N1-C13-C14 | 120.7 |

(continued on next page)
listed in Table 4, where orbital energies, energy band gap and reactivity descriptors (like electron affinity, chemical softness, ionization potential, chemical softness... ...) are reported. The gap between two energetic states describes the molecular chemical reactivity. The energies of the four important FMOs (HOMO, HOMO -1, LUMO and LUMO + 1) were calculated via the TD-DFT approach with B3LYP/6-31G* level. Their 3D plots are illustrated in Figs. 3 and 4. It is clear from the figure of the chloroquine molecule that the HOMO and LUMO orbitals are localized essentially on the benzene and pyridine rings. The green color represents the negative phase; on the other hand the red color corresponds to the positive phase which is well clarified in the density of states (DOS) spectrum (Fig. 5). DOS spectrums characterize the energy levels per unit energy increment and its composing in energy. The displaying study per orbital shows that the green and the red lines in these curves correspond to the HOMO and LUMO energy levels, respectively. As a result, the energy level of the HOMO orbital is about 5.594 eV and the energy level of the LUMO orbital is about 1.115 eV. The HOMO-LUMO gap energy (Eg) of the chloroquine is equal to 4.479 eV. This low energy value promotes the transfer of electrons in the chloroquine molecule. These values are compatible with those obtained by the DOS spectrum. The state HOMO-1 form another set of degenerate orbital 5.747 eV lower in energy than the HOMO set. As shown for the

Table 4
Calculated of some global reactivity descriptors of chloroquine derivatives.

| Parameters             | Chloroquine | Chloroquine phosphate |
|------------------------|-------------|-----------------------|
| ELUMO                  | -1.115      | -2.599                |
| EHOMO                  | -5.594      | -5.228                |
| EHOMO - ELUMO          | -4.477      | -2.629                |
| E(LUMO -1)             | -0.375      | -1.579                |
| EHOMO-1                | -5.747      | -5.473                |
| EHOMO+1 - ELUMO+1      | -5.372      | -3.894                |
| Reactivity descriptors |             |                       |
| Ionization potential (I) | 5.594      | 5.228                |
| Electron affinity (A)  | 1.115      | 2.599                |
| Chemical hardness (η)  | 2.239      | 2.629                |
| Chemical softness (ζ)  | 1.1915     | 1.3145               |
| Electronegativity (χ)  | 3.3545     | 3.9135               |
| Chemical potential     | -3.3545    | -3.9135               |
| Electrophilicity index (ω) | 2.512   | 2.912                |
| Maximum charge transfer index | 1.498 | 1.488                |

I = -E(HOMO), A = -ELUMO. η = [(I - A)/2, ζ = 1/2], χ = (1 + A)/(2, , μ = -(1 + A)/(2, μ = μ2)/(21) and ΔNmax. = -μ/η.}

Fig. 3. The atomic orbital compositions of the HOMO, HOMO-1, LUMO and LUMO + 1 frontier molecular orbitals for chloroquine molecule.
chloroquine phosphate, LUMO orbital lying at $-2.59$ eV, located on all the atoms of the benzene and pyridine rings. The HOMO orbital is lying at $-5.228$ eV. Consequently, $E_g$ is closed to $-2.629$ eV. The change observed here in the gap value from $-4.479$ eV to $-2.629$ eV in solution involves an expected high reactivity for the chloroquine phosphate. This decrease in gap energy makes the flow of electrons easier, so the molecule becomes soft and more reactive. We can also note that the chloroquine molecule is harder before adding the phosphate groups, given the energy value of gap. This result is in agreement with the strong increase in the dipole moment value of 6.05 Debye (of chloroquine) to 24.49 Debye (of chloroquine phosphate).

Using the energies of FMOs, we calculated the reactivity descriptors of chloroquine and chloroquine phosphate molecules. $A = -E_{\text{LUMO}}$ represent the electron affinity; $I = -E_{\text{HOMO}}$ represent the ionization potential and $\mu = 1/2(I + A)$ is the electronic chemical potential. The chemical hardness ($\eta$) is found to be 2.239 and 2.629 eV for chloroquine and chloroquine phosphate, respectively. The chemical softness ($\zeta$) has been computed and found to be 1.1195 and 1.3145 eV$^{-1}$. Moreover, the electrophilicity index ($\omega$) is about 2.512 eV for chloroquine and 2.912 eV for chloroquine phosphate. Based on the value found of the electrophilicity index, we can conclude that the chloroquine phosphate is a good electrophile better than chloroquine. Therefore, it is able to accept an electron doublet in order to form bonds with another reagent which is necessarily a nucleophile. Electronegativity is also determined ($\chi = (I + A)/2$) and it is found to be $\chi_{\text{chloroquine}} = 3.3545$ eV and $\chi_{\text{chloroquine phosphate}} = 3.9135$ eV.

3.3. Molecular electrostatic potential

The molecular electrostatic potential (MEP) is a well-established tool for the study of molecular reactive properties and to describe intermolecular interactions (Reed and Weinhold, 1985). It allows us to search the most reactive nucleophilic and electrophilic sites of a molecule against the reactive biological potentials (Gökce et al., 2013). These sites promote the formation of hydrogen bonds. The electrophilic site indicates a strong attraction, while the nucleophilic site indicates a strong repulsion. The electrostatic potential diagrams of chloroquine and chloroquine phosphate are illustrated in Fig. 6 at B3LYP/6-31G* method. MEP diagram gives negative, positive and neutral electrostatic potential regions in terms of color grading and is an indicator in the research of molecular structure properties. The red color represents the most electronegative electrostatic potential. That is, atoms in this region have a tendency to attract electrons (electrophilic). The blue color indicates the most electropositive potential (strong attraction) and the red color indicates the most electronegative potential (strong repulsion). Regions where the potentials are zero are denoted by green color. As a results, MEP surfaces varies between $-5.504$ $0.116$ a.u (deepest red) to $5.504$ $0.116$ a.u (deepest blue) for chloroquine and between $-0.116$ a.u to $0.116$ a.u for chloroquine phosphate. As can be seen, the MEP map of chloroquine molecule (Fig. 6a), a maximum positive region is localized on the...
nitrogen N and hydrogen H atoms indicating a possible site for the binding of a ligand to a receptor (Duhovny et al., 2002; Seeliger and de Groot, 2010; Amin et al., 2010; Ahmed et al., 2013; Ghalla et al., 2018). In our case, the receptor represents the COVID-19 protein which has one or more specific active sites, more or less accessible. At each step, the interactions are affected and the best pose of the ligands is determined. 10 poses have been obtained; we have chosen the best pose with the lowest energy. These best poses, as presented in Fig. 7, were selected for investigating the different types of interactions that introduce a biological signal.

3.4.1. Chloroquine

The examination of Table 5 revealed that the chloroquine ligand presents the highest total energy score with the target protein 6 M03 which is equal to $-8.186$ kcal/mol. Note that the total energy is the sum of the three energies interactions: VDW, hydrogen bond and electronic. Van der Waals interaction is a potential energy of attraction between two molecules. It represents the sum of the energies of Keesom, London and Debye. The H-bond represents an interaction between two electronegative atoms. Generally, the energy of an H-bond is of the order of a few tens of KJ/Mol. It varies between 1 and 60 KJ/mol for neutral fragments, and sometimes it can reach higher values for some covalent bonds. The last interaction is electronic; they always take very low values compared to the other two interactions.

Chloroquine ligand presents the strongest van der Waals interaction $E_{\text{VDW}} = -75.581$ kcal/mol. The docking pose analysis showed that the chloroquine ligand is oriented with the VDW interactions surrounded by the chains of LEU-141, MET-165, PHE140, HIS163, GLN189, MET49, GLY143, THR25 and VAL42 binding residues in the 6 M03 protein. Also, it has the strongest H-bond interaction $E_{H-bond} = -6.893$ kcal/mol. The greater negative energy score suggests a more favorable binding mode. Table 6 presents the different interactions between the chloroquine ligand and proteins via the binding residues along with their bond length. Results obtained for protein targets show that the chloroquine ligand has bonded effectively with 6 M03 target sites with two remarkable carbon-hydrogen bond interactions. The mentioned compound is immersed in a hydrophobic environment surrounded by the chains of LEU-141, MET-165, PHE140, HIS163, and CYS145 were formed with bond lengths 4.42 and 4.03 Å. C15 atom made two Alkyl interactions with A:CYS145 and A:LEU27 residues and having distances 3.99, 4.03 Å, respectively. These results have been well described in Figs. 8 and 9. Furthermore, chloroquine molecule showed total energy score of $-77.498$ kcal/mol against 5R7Y protein with VDW interaction ($-70.605$ kcal/mol) and hydrogen bond energy ($-6.893$ kcal/mol). Regarding the two other proteins (5R81 and 6LU7), the interaction energies are slightly weaker in comparison with the other ligands but as even important remain. The docking calculations led to the following results: the total energies scores are equal to $-68.514$ kcal/mol and $-67.136$ kcal/mol for 5R81 and 6LU7, respectively. The van der Waals interactions were found to be $E_{\text{VDW}}$ (for 5R81) = $-65.014$ kcal/mol and $E_{\text{VDW}}$ (for 6LU7) = $-64.988$ kcal/mol. Additionally, the hydrogen bond interactions exhibiting values of $-3.500$ and $-2.147$ kcal/mol for 5R81 and 6LU7 receptors. In the chloroquine-5R7Y complex, a Pi-Anion and Pi-Sulfur interactions wrapped by the amino acids GLU166 and CYS145 were formed with bond lengths 4.42 and 4.03 Å. C15 atom made two Alkyl interactions with A:CYS145 and A:LEU27 residues and having distances 3.99, 4.07 Å. Also, C15 interact with A:HIS41 via a Pi-Alkyl interaction (bond length = 3.88 Å). A:SER144 and A:HIS164 amino residues form two carbon-hydrogen bond interactions with H46 and H27 atoms. Their bonding distances are found to be 2.61 Å and 1.89 Å, respectively. In 5R81virus, A:MET165 and A:MET49 amino residues are involved in the alkyl interaction with C10 and C15 atoms having bond length 4.43 and 3.96 Å. Pyridine group formed Pi-Alkyl, Pi-Sulphur and Pi-Donor hydrogen bond interactions with A:LEU27 (5.13 Å), A:CYS145 and A:GLY143.
Another Pi-Alkyl interaction is also seen which contributed by A:HIS41 with C15 atom, indicating distance 4.25 Å. For the last ligand 6LU7, the LEU141 (2.38 Å), the ASN142 (3.02 Å) and the HIS163 (2.47 Å) amino acids formed a C–H bond interactions with H29, H27 and H28 atoms of chloroquine. In addition to these weak interactions there are two alkyl interactions; one between PRO168 residues and the CI atom and the second one is in between CYS145 and the N2 atom, indicating bond distance 3.63 and 4.35 Å, respectively. Subsequently, the H30 atom exhibit a conventional-H bond interaction with GLU166 residues and bonding distance is 2.22 Å.

In order to upgrade the recognition of the interactions existing between receptor and ligand, the affinities of these complexes were calculated by using AutoDockTools (ADT) (Morris et al., 2008). These affinities describe the strength of a non-covalent interaction between the ligand and its target which binding to a site on its surface. It is premised on the numeral and the nature of the physicochemical interactions. As illustrated in Table 5; the affinities values (in ultimate value) of chloroquine are found to be in the order of 6.7 > 6.6 > 6.1 kcal/mol for (6 M03 and 5R81), 5R7Y and 6LU7, respectively.

3.4.2. Chloroquine phosphate

According to the energetic related results of the docking calculations and the corresponding docking positions, the chloroquine phosphate has better binding interaction with 5R7Y protein (as seen in Table 5 and Fig. 7). This protein strongly interacts with the mentioned ligand, resulting in high inhibition potency. It
as shown in Table 7, the amino acid A:MET49 and A:MET165 residues were involved in alkyl interaction with C15/C0 interaction were equal to C15 atom was linked to A:HIS41 (4.40 Å) throughout pi-alkyl interaction with 4.52 and 4.39 Å bond length, respectively. Likewise, A:SER144 and A:HIS164 residues with distance value 2.74 Å and their VDW interaction were −79.862 and −69.861 kcal/mol, respectively. For PDB ID: 5R7Y, as shown in Table 7, the amino acid A:MET49 and A:MET165 residues were involved in alkyl interaction with C15 atom with 4.52 and 4.39 Å bond length, respectively. Likewise, C15 atom was linked to A:HIS41 (4.40 Å) throughout pi-alkyl interaction. Moreover, oxygen atom O55 showed a conventional hydrogen bond with amino acid A:GLU166 having distance 4.19 Å bond length. For the second 6 M03-chloroquine phosphate complex, A:MET49 interacted with C22 and C30 atoms via alkyl interaction with 3.17 and 4.05 Å bond length. A pi-alkyl interaction was also being formed between A:HIS41 residues and C20 (3.58 Å). In addition, H63 atom (2.45 Å) involve in carbon H-bond with A:GLU164 amino acid. The pyridine ring exhibited pi-donor interaction with A:LEU141 and A:HIS145 via Alkyl interaction with 3.54 Å distance. The benzene ring (4.73 Å) for PDB ID: 6LU7. As well, the Cl atom interacts with A:HIS145 via Pi-Alkyl interactions with Cl atom (4.87 Å) and benzene ring (4.73 Å) for PDB ID: 6LU7. As well, the Cl atom interacts with A:HIS145 via Pi-Alkyl interactions with Cl atom (4.87 Å) and benzene ring (4.73 Å) for PDB ID: 6LU7.
The results obtained show that the chloroquine penetrates well into the active areas of the protein. Therefore, it can be considered to be a potent inhibitor against COVID-19 diseases. But the chloroquine phosphate molecule showed a better activity rather than chloroquine since it interacts stronger with the receptor. This can be justified by the effect of the addition of the phosphate groups.

3.5. Hybridization effect

Of course, each compound has its own characteristics that distinguish it from the rest. The chloroquine phosphate is initially made up of chloroquine. Evidently, the adding of other atoms in the geometry of the chloroquine has an influence on their stability. The chloroquine compound becomes more stable when adding the phosphate groups since the global minimum energy decreases. Moreover, the smallest dipole moment was obtained for the chloroquine whereas the highest one was obtained for the chloroquine phosphate. This increase shows that the chloroquine is harder before adding the phosphate groups and also it promotes the formation of hydrogen bonds. We also find that by adding phosphate group the gap energy decreases, which involves a high reactivity for the chloroquine phosphate. This decrease in gap energy makes the flow of electrons easier, so the molecule becomes soft and more reactive.

4. Conclusion

Given their high efficiency in the treatment against COVID-19 pandemic, chloroquine derivatives have been studied combining DFT method and molecular docking calculations. The optimized molecular structures of chloroquine and chloroquine phosphate have been carried out using DFT/B3LYP/6-31G* method and their geometrical parameters were also determined. The comparison of the observed and calculated results showed a good agreement. Molecular properties such as frontiers orbitals, gap energies and reactivity descriptors have also been discussed. Results reveal that the addition of the sulfate group resulted in a decrease in the gap energy, which involves an expected high reactivity for the chloroquine phosphate. This decrease in gap energy makes the flow of...
electrons easier, so the molecule becomes soft and more reactive. The density of states (DOS) was determined and it allowed better describing the border orbitals. Thereafter, the calculated MEP maps show the positive potential sites are favorable for nucleophilic attack, whereas the negative potential sites are favorable for the electrophilic attack. Docking results were discussed based on the different interactions between the ligands and proteins. The chloroquine derivatives are found to be a good inhibitor of COVID-19 virus and can, therefore, be effective in controlling this disease. We found that chloroquine phosphate was considered to be the best inhibitor of coronavirus pandemic.

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**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
Table 7
Amino acid residues-chloroquine phosphate interactions.

| Ligand        | Target protein | Binding residue | Type          | Atoms | Bond length (Å) | Interactions       |
|---------------|----------------|-----------------|---------------|-------|-----------------|--------------------|
| Chloroquine phosphate 5R7Y | A:MET49 | Methionine | C₁₅ | 4.52 | Alkyl           |
|                | A:MET165 | Methionine | C₁₅ | 4.39 | Alkyl           |
|                | A:MET165 | Methionine | C₁₅ | 4.40 | Pi-Alkyl        |
|                | A:GLU166 | Glutamic Acid Asparagine | O₅₅ | 2.65 | Conventional H-bond |
|                | A:ASN142 | Pyridine | C₂₀ | 4.19 | Pi-Donor H-bond |
| 5R81-Chloroquine phosphate | A:MET49 | Methionine | C₂₂ | 3.17 | Alkyl           |
|                | A:MET49 | Methionine | C₂₀ | 4.05 | Alkyl           |
|                | A:HIS41 | Histidine | C₂₀ | 3.58 | Pi-Alkyl        |
|                | A:HIS164 | Histidine | H₀₃ | 2.45 | Carbon H-bond   |

(continued on next page)
Table 7 (continued)

| Ligand | Target protein | Binding residue | Type | Aoms | Bond length (Å) | Interactions |
|--------|----------------|-----------------|------|------|----------------|--------------|
| A:ASN | Asparagine | 3.79 | P-Donor H-bond |
| A:Glu166 | Glutamic Acid | 3.27 | Conventional H-bond |
| A:His145 | Histidine | 4.87 | P-Alkyl |
| A:His145 | Histidine | 4.73 | P-Alkyl |
| A:His145 | Histidine | 3.54 | Alkyl |
| A:Glu189 | Glutamin | 2.74 | Carbon-hydrogen bond |
| A:His163 | Histidine | 2.95 | Carbon-hydrogen bond |
| A:ASN | Asparagine | 2.78 | Conventional H-bond |
| A:SER | Serine | 2.93 | |
| A:PRO | Proline | 5.02 | Alkyl |
| A:MET | Methionine | 4.40 | P-Alkyl |
| A:MET | Methionine | 4.67 | P-Alkyl |
| A:HIS | Histidine | 3.81 | P-Sigma |
| A:THR | Threonine | 3.04 | Halogen |
| A:HIS | Histidine | 5.01 | P-Ti shaped |

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