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Chloroquine and hydroxychloroquine inhibitors for COVID-19 sialic acid cellular receptor: Structure, hirshfeld atomic charge analysis and solvent effect

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A B S T R A C T

COVID-19, the pandemic disease recently discovered in Wuhan (China), severely spread and affected both social and economic activity all over the world. Attempts to find an effective vaccine are challenging, time-consuming though interminable. Hence, re-proposing effective drugs is reliable and effective alternative. Taking into account the genome similarity of COVID-19 with SARS-CoV, drugs with safety profiles could be fast solution. Clinical trials encouraged the use of Chloroquine and Hydroxychloroquine for COVID-19 inhibition. One of the possible inhibition pathways is the competitive binding with the angiotension-converting enzyme-2 (ACE-2), in particular with the cellular Sialic acid (Neu5Ac). Here, we investigate the possible binding mechanism of ClQ and ClQOH with sialic acid both in the gas phase and in water using density functional theory (DFT). We investigated the binding of the neutral, monoprotonated ClQs and ClQOHs to sialic acid to simulate the pH effect on the cellular receptor binding. DFT results reveals that monoprotonated ClQ+ and ClQOH+, which account for more than 66% in the solution, possess high reactivity and binding towards sialic acid. The Neu5Ac–ClQ and the analogous Neu5Ac–ClQOH adducts were stabilized in water than in the gas phase. The molecular complexes stabilize by strong hydrogen bonding and π–π stacking forces. In addition, proton-transfer in Neu5Ac–ClQOH+ provides more stabilizing power and cellular recognition binding forces. These results shed light on possible recognition mechanism and help future breakthroughs for COVID-19 inhibitors.

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1. Introduction

COVID-19 pandemic disease severely affects both social and economic activity around the world. The seventh coronavirus COVID-19 (SARS-CoV 2) identified at the late 2019 in Wuhan City, China has been a world pandemic infection. The Beta coronavirus SARS-CoV 2 shared more than 76 % of amino acids with the acute respiratory syndrome coronavirus (SARS-CoV) [1, 2]. Hence, the viral target of both pathogens expected to be similar and inhibiting by the same drugs. Chloroquine (ClQ) and hydroxychloroquine have been known for long time as active drugs for Malaria treatment and most coronaviruses including SARS-CoV [3–5]. Recently, clinical trials proved the effective use of both ClQ and ClQOH for the treatment of SARS-CoV-2 [6–10]. The activity mode of ClQ involved different steps inside and outside the human cell. On one hand, Chloroquine modulates the intracellular pH environment [3, 6]. In the absence of the inhibitor and low pH, the virus particles are uncoated and liberating the viral genome inside the human cell [11]. However, in presence of suitable inhibitor, such as ClQ, the rapid elevation of the endosomal pH prevents the virus-endosome fusion and blocked the virus replication process.

SARS-CoV-1 attached to the cellular receptor angiotensin-converting enzyme 2 (ACE2) through the spike protein [12]. ClQ show an antiviral effect against SARS-CoV-1 when the cells treated with the drug either before or after the exposure to the virus [3], which suggest that ClQ interfere with the virus binding receptor to the cell (ACE2) [3, 13]. In addition, ClQ inhibit the quinone reductase, which is the dominant factor for the biosynthesis of sialic
acids [14]. Sialic acid is a monosaccharide expressed on the surface of vertebrates cells and carry a formal negative charge [15]. The ubiquitous presence of Sialic acid on the cell surface illustrates its importance in the biophysical properties of the cell, including the intracellular interactions and immune system [15, 16]. CIQ inhibit the activity of different human viruses such as HCoV-O43 and orthomyxoviruses through the interference with sialic acid biosynthesis [17]. Sialic acid exists on the glycan terminal of ACE2 receptor and determined as potential receptor for coronaviruses [18]. Investigation of the molecular mechanism between sialic acid (Neu5Ac) with CIQ and CIQOH gives more inside for the molecular recognition. In addition, the detailed mechanism contributes for the future investigation to COVID-19 potential inhibitors. Attempts have been reported to study the molecular mechanism between the drug molecules and SARS-CoV-2 spike-ACE2 complex [19–22].

Here, we used theoretical calculations through density functional theory (DFT) with B3LYP level and 6-311+g(d,p) basis set to investigate the molecular binding and recognition parameters between Neu5Ac and CIQ and CIQOH drugs. In order to investigate the effect of pH on the binding mode, neutral, monoprotonated, and diprotonated forms of the drugs accounts for different pH values were explored. Stabilization of the investigated drugs form and the corresponding complexes were accounted in water using conductor-like polarizable continuum model. The stabilization forces for the binding of Neu5Ac and CIQ and CIQOH were investigated. The molecular adducts Neu5Ac-CIQs and Neu5Ac-CIQOHs stabilized by hydrogen bonding (HB) and vdW forces. In addition, the monoprotonated Neu5Ac-CIQOH+ adduct show unique proton transfer from CIQOH+ to the carboxylic group on Neu5Ac surface, which might account for the unique inhibition of COVID-19 by hydroxychloroquine in alkaline medium.

2. Computational details

The structures of the investigated molecules were constructed by Gaussian view 6. Then, molecules were optimized by Gaussian 09 program [23]. The optimization process were performed using B3LYP level with 6-311++g(d,p) basis set. The energies were refined using wB97XD that account for long-range interaction and dispersion forces together with Def2tzvpp basis set [24, 25]. The structures were optimized using the conductor-like polarizable continuum model (PCPM), which consider one of the best solvation model, to simulate the interaction of the investigated compounds with water [26]. In order to investigate the Noncovalent interactions (NCI), visualize the reduced density gradient (RDG), and calculate the Hirshfeld charge, Multiwfn software 3.5 [27] were used together with VMD program [28]. The binding energy of the adducts was calculated as:

$$E_{\text{binding}}(\text{Neu5Ac} - \text{CIQ}) = E_{\text{Neu5Ac-CIQ}} - (E_{\text{Neu5Ac}} + E_{\text{CIQ}})$$

Where $E_{\text{Neu5Ac-CIQ}}$, $E_{\text{Neu5Ac}}$ and $E_{\text{CIQ}}$ are the electronic energies of Neu5Ac-CIQ, Neu5Ac and CIQ respectively.

3. Results and discussion

3.1. Optimized structures

Sialic acid (Neu5Ac) surface recognition to the cell hosts largely depends on the ionic interactions. Neu5Ac has surface carboxylic group with $pK_a$ value of 6.7, which dominate surface recognition and ligand binding affinity [29]. At pH higher than the $pK_a$ value, carboxylic group deprotonated to form the carboxylate ion, which facilitate ligand recognition through nucleophilic reactions. The structure of Neu5Ac, pH higher than the $pK_a$ value, in the gas phase and the molecular electrostatic potential (MEP) calculated at B3LYP/6-311++g(d,p) level shown in Fig. 1. The optimized structure shows that carboxylate and hydroxyl groups dominate Neu5Ac surface. The Neu5Ac structure in water was more stable than the gas phase by -20.55 kcal/mole. The MEP of Neu5Ac shows the presence of different nucleophilic sites with negative electrostatic potentials ranges from -50 to -87 kcal/mol (Fig. 1b). These sites are potential cellular receptors for competitive binding of either drug molecules or viruses- S-protein. TD-DFT calculations were used to determine both HOMO and LUMO orbitals in order to determine the electron-donating sites on Neu5Ac surface (Fig. 1c and d). The HOMO orbital of Neu5Ac (electron-donating site) locates on the carboxylate group that is proposed as nucleophilic site.

CIQ and CIQOH are dibasic saccharides ($pK_{a1} = 8.1$ and $pK_{a2} = 10.2$) that possess a monoprotonated and diprotonated form (Scheme 1). Based on Henderson-Hasselbalch equation, at pH 6.4 more than 98% presence as CIQ++, where only ~2% as of CIQ+ [29–31]. While the CIQ++ decreases to ~94% and CIQ+ increases to 6% at physiological pH values (pH 6.9). In basic medium, for example at pH 8.4, the monoprotonated (CIQ+) increases to ~66% and the diprotonated decreases to less than 34%. Hence, the molecular interaction between different forms of CIQ and CIQOH with Neu5Ac contributes to the understanding of structure-activity relationships. The optimized structure of CIQ and CIQOH together with the MEP are shown in Figs. 2 and 3. The corresponding monoprotonated and diprotonated structures are shown in S1-S4. CIQ and CIQOH structures show planar conformation, where the dehedral angle (C18-N17H-C7-C3 ~179°) (Figs. 2 and 3). The MEP of CIQ (Fig. 2b) shows the presence of nucleophilic sites (~30.7 kcal/mole) on the quinoline aromatic nitrogen atom, where MEP of CIQOH (Fig. 3b) shows the presence of an extra electrophilic site on the OH group. The CIQ compounds were more stable in water than in the gas phase in the order of CIQ < CIQ+ < CIQ++. However, in analogy, the CIQOH forms were more stable in water where the diprotonated form was the most stable (Table 1).

3.2. Energy gap analysis

In order to calculate the energy gap of the investigated compounds, TD-DFT at the optimized structures were performed. The
Fig. 1. a) optimized structure, b) MEP, c) HOMO and d) LUMO of Neu5Ac calculated at B3LYP/6-311++g(d,p) level of theory in the gas phase.

Fig. 2. a) optimized structure of ClQ and b) the MEP of ClQ calculated at B3LYP/6-311++g(d,p) in the gas phase.

Fig. 3. a) optimized structure of ClQOH and b) the MEP of ClQOH calculated at B3LYP/6-311++g(d,p) in the gas phase.

|                        | Gas phase | H2O | |                        | Gas phase | H2O | |                        | Gas phase | H2O | |
|------------------------|-----------|-----|---|------------------------|-----------|-----|---|------------------------|-----------|-----|---|
|                        | $\varepsilon_{\text{HOMO}}$ (eV) | $\varepsilon_{\text{LUMO}}$ (eV) | $\Delta\varepsilon$ (eV) | $\varepsilon_{\text{HOMO}}$ (eV) | $\varepsilon_{\text{LUMO}}$ (eV) | $\Delta\varepsilon$ (eV) | $E_{\text{water}} - E_{\text{gas phase}}$ kcal/mole | $E_{\text{water}} - E_{\text{gas phase}}$ kcal/mole |
| Neu5Ac                 | -7.02     | -1.01 | 6.01 | -6.28 | -0.90 | 5.38 | -20.55 (-11.2)          |
| ClQ                    | -5.96     | -1.58 | 4.38 | -4.96 | -1.69 | 3.27 | -7.98 (-4.12)           |
| ClQ$^+$                | -7.90     | -5.93 | 1.97 | -5.04 | -3.62 | 1.42 | -4.94 (-14.6)           |
| ClQ$^{++}$             | -12.29    | -7.83 | 4.47 | -6.10 | -2.68 | 3.42 | -48.98 (-14.9)          |
| HClQ                   | -5.99     | -1.60 | 4.39 | -5.36 | -1.40 | 3.96 | -8.87 (-3.8)            |
| HClQ$^+$               | -8.04     | -5.95 | 2.09 | -7.61 | -5.85 | 1.76 | -45.54 (-15.1)          |
| HClQ$^{++}$            | -12.25    | -7.79 | 4.46 | -11.85 | -7.89 | 3.96 | -49.19 (-15.9)          |

* Energies calculated at wB97XD/Def2tzvpp level of theory.
HOMO orbital of Neu5Ac was situated on the carboxylate group, while the LUMO orbital was positioned on hydroxyl moiety. Accordingly, the carboxylate group could be the possible donating site when the interaction with any surface molecules is initiated. The HOMO orbitals of the CIQ, CIQ+ and CIQ++ were located on the aromatic ring, while the CIQ+ HOMO orbital was situated on the substituted alkyl terminal group. The LUMO orbital of CIQ, CIQ+ and CIQ++ was situated on the aromatic quinoline ring, which is the potential site for accepting electron when encountered the reaction with Neu5Ac molecule (Fig. 4). In analogy, the LUMO orbitals of CIQOH, the electron acceptor sites, were positioned on the aromatic quinoline ring (Fig. 5). The calculated energy gap for the CIQs structures were in the order of the order CIQ+ < CIQ < CIQ++, which decreases in the same order in H2O (Table 1). This implies that CIQ+ is the most reactive electrophilic form for the reaction with Neu5Ac [32, 33]. Table 1 shows that the calculated energy gap for CIQOH structures were in the order CIQOH+ < CIQOH < CIQOH++. This result shows that the CIQOH+ is the most active form both in gas phase and in water [33].

3.3. Molecular binding of Neu5Ac with CIQs and CIQOHs

Based on the calculated HOMO and LUMO orbitals of Neu5Ac and CIQs and CIQOHs, Neu5Ac was the potential electron-donating site and CIQs and CIQOHs were the electron-accepting molecules. Non-covalent interactions such as hydrogen bonding, halogen bonding, and vdW forces have been known for the assembly of and molecular recognition binding [22,34–36]. The optimized structure of the molecular adducts show the products were stabilized by different non-covalent interactions such as HB [22, 37, 38]. For example, the Neu5Ac-CIQ+ structure (Fig. 6a) stabilized by strong hydrogen bonding between the Neu5Ac OH group and the quinoline nitrogen aromatic ring (N62-H88...O21, d=1.82 Å and N62-H88...O21 =157.5°) and H65...O10 (d=2.24 Å, and C44-H65...O10 = 145.6°) [22]. In addition, the short contact between the O11...C63 (d=3.37 Å), assigned to the π–π interactions (Fig. 6a and b) [22]. The binding energy of Neu5Ac-CIQ+ was -8.5 kcal/mol. In H2O, the HB distance was shorter (N62-H88...O21, d=1.77 Å) and more directional (N62-H88...O21 =157.5°). In addition, the binding constant of the Neu5Ac-CIQ+ in water increases (-26.2 kcal/mol). Similarly, the optimized structures of Neu5Ac-CIQ and Neu5Ac-CIQ++ stabilized by hydrogen bonding and π–π forces (Figs. S5–S7).

Neu5Ac-CIQOH+ showed the presence of two stable structures; Neu5Ac-CIQOH+–I and Neu5Ac-CIQOH+–II. Fig. 7 shows the most stable structures of Neu5Ac-CIQOH+–I. The Neu5Ac-CIQOH+–I structure stabilized by the intermolecular proton transfer from the protonated quinoline nitrogen atom (N62) to the carboxylate O10 atom, which is domanated for the enzyme and cellular recognition inhibition process [39–41]. The N62-H85 bond distance increased to 1.64 Å, where the O10-H85 bond distance approached 1.02 Å. In addition strong hydrogen bonding C59-H60...O11 (d=2.28 Å, and C59-H60...O11 = 162.9°) (Fig. 7a) was observed. The proton-transfer process was facilitated by the increasing negative charge on carboxylic group and the oriented bond angle.

The binding energy of Neu5Ac-CIQOH+ was -14.24 kcal/mol in the gas phase. In H2O, the N62-H85 distance was increased (d=1.68 Å) and more directional (N62...H85-O10 = 178 Å), whereas the O10-H85 hydrogen bond was slightly decreases (d=0.99 Å). The binding constant of the Neu5Ac-CIQOH+ (Table 2) in water increased (-20.4 kcal/mol), which attributed to the decreasing the proton-transfer energy barrier in presence of water molecules [42, 43]. However, Neu5Ac-CIQOH+–II was stabilized by a set of hydrogen bonding and vdW short contact, which facilitate the encapsulation of Neu5Ac by CIQOH+ (Fig. 8) [34]. The Neu5Ac-CIQOH+–I was more stable than Neu5Ac-CIQOH+–II by 8.1 kcal/mol.

3.4. Hirshfeld atomic charges analysis

To calculate the nature and direction of charge transfer, Hirshfeld atomic charges, which based on the electronic density at atoms, were calculated for the molecular adducts between Neu5Ac
Fig. 5. Calculated HOMO (left) and LUMO (right) orbitals of a) ClQOH, b) ClQOH+, and c) ClQOH++ at B3LYP/6-311++g(d,p).

Fig. 6. a) optimized structure of Neu5Ac-CIQ+ and b) vdW surface of Neu5Ac-CIQ+ adduct calculated at B3LYP/6-311++g(d,p).

Table 2
Calculated binding energies, HOMO, LUMO orbitals of Neu5Ac-CIQ and Neu5Ac-CIQOH structures in the gas phase and water.

|            | Gas phase | H2O |
|------------|-----------|-----|
|             | E<sub>binding</sub>kcal/mol | E<sub>HOMO</sub> (eV) | E<sub>LUMO</sub> (eV) | ΔE(eV) | E<sub>binding</sub>kcal/mol | E<sub>HOMO</sub> (eV) | E<sub>LUMO</sub> (eV) | ΔE(eV) |
| Neu5Ac-CIQ  | -8.1(-4.1) | -3.32 | 1.01 | 4.33 | -11.6(-5.3) | -5.76 | -1.50 | 4.26 |
| Neu5Ac-CIQ+ | -8.5(-4.3) | -5.73 | -2.54 | 3.19 | -26.2(-6.4) | -5.81 | -1.56 | 4.23 |
| Neu5Ac-CIQ++| -9.0(-4.9) | -8.11 | -4.90 | 3.21 | -34.8(-7.5) | -6.76 | -2.49 | 4.27 |
| Neu5Ac-HCIQ | -12.7(-5.9) | -3.34 | 0.98 | 4.32 | -13.78(-6.1) | -5.77 | -1.50 | 4.27 |
| Neu5Ac-HCIQ- | -14.24(-6.2) | -5.38 | -2.07 | 3.31 | -20.26(-6.8) | -5.04 | -1.84 | 3.20 |
| Neu5Ac-HCIQ++| -18.39(-7.8) | -8.13 | -3.93 | 4.2 | -23.39(-7.9) | -6.75 | -2.49 | 4.26 |

* Energies calculated at wB97XD/Def2tZvpp level of theory.
and CIQs and CIQOHs different forms [44, 45]. Hirshfeld atomic charges analysis is reliable method to accurately determine both nucleophilic and electrophilic sites [46]. Table 3 shows the calculated Hirshfeld charges together with the change in the charge transfers quantity on Neu5Ac fragment. The data in Table 3 shows that in Neu5Ac-CIQs and Neu5Ac-CIQOHs, the Neu5Ac was the electron-donating fragments both in the gas phase and water. In case of CIQ adducts, the change in charge transfer quantity (ΔQ) increases as CIQ < CIQ+ < CIQ+++, which indicate the stabilization of the formed adducts in the same order. However, in CIQOH adducts, the monoprotonated (Neu5Ac-CIQOH+) shows higher ΔQ, which indicate the more stabilization adducts. The ΔQ values were in the order CIQ+ < CIQ+++ < CIQOH++. To validate the electron donating nature of Neu5Ac, CHELPG method for calculating the atomic charges based on electrostatic potential were used. Results in Table 3 shows a good agreement between the calculated charges on Neu5Ac and the charge transfer amount by both Hirshfeld and CHELPG atomic charge methods.

Table 3 shows the calculated dipole moment for the molecular adducts of Neu5Ac-CIQs and Neu5Ac-CIQOHs structures. The dipole moment of the investigated adducts increased in the aqueous solution, which attributed to the increase of the polar nature of the complexes in H2O [47]. This indicates that aqueous solution facilitates the charge-transfer and stabilizes the molecular complexes [35]. In Neu5Ac-CIQs and Neu5Ac-CIQOHs molecular adducts, both the binding energies and the dipole moment of adducts increases with the increase in the ΔQ values in the gas phase as well as in water (Figs. 9 and 10). Interestingly, the monoprotonated Neu5Ac-CIQ+ and Neu5Ac-CIQOH+ possess the lower Egap, which confirms the unique stabilization of adducts.


### 3.5. Noncovalent interaction

Neu5Ac interacts with both CIQ and CIQOH to form the corresponding molecular complexes Neu5Ac-CIQs and Neu5Ac-CIQOHs adducts. In order to investigate the nature of the stabilization forces, non-covalent interaction calculation, which based on the visualizing the electron density, were performed [27]. The Neu5Ac-CIQs and Neu5Ac-CIQOHs molecular complexes stabilized by hydrogen bonding in addition to the Van der Waals (vdW) forces. The NCI isosurface plot (0.7 a.u) of CIQ and CIQOH forms are shown in Figs. S8-S9). For example, in Neu5Ac-CIQ+, strong hydrogen bonding is observed (blue isosurface region) between the protonated quinolone nitrogen atom in CIQ and O atom from the Neu5Ac (Fig. 11a). Relatively weak hydrogen bond was observed for the carboxylate group (green isosurface region). Additional stabilization forces were observed by the short contacts of carboxylate group of Neu5Ac and the CIQ+ aromatic moiety (vdW) forces. In case of Neu5Ac-CIQOH+, the adduct stabilization forces was dominated by the strong hydrogen bonding between the carboxylate group and the protonated N-H group of the CIQOH+ aromatic moiety (Fig. 11b).

### 3.6. Fukui function analysis

In order to explore the reactivity of the individual atoms, Fukui function was analyzed for the optimized molecules at B3LYP/6-311++g(d,p). Fukui function is a powerful method to detect the ability of individual atoms as donor or acceptor sites [48]. The electrophilic and nucleophilic nature of atoms determined by Eqs. (1)-(3):

\[
f^-(r) = q_j(N) - q_j(N-1) \tag{1}
\]

\[
f^+(r) = q_j(N + 1) - r_j(N) \tag{2}
\]

\[
f^0(r) = \frac{1}{2}[q_j(N + 1) - q_j(N - 1)] \tag{3}
\]

In these equations, \( f^- (r) \), \( f^+ (r) \), and \( f^0 (r) \) refers to electrophilic, nucleophilic and free radical respectively. The atomic charge on the \( j \)th atomic sites \( q_j \) was positioned on neutral \( (N) \), anionic \( (N+1) \), and cationic \( (N-1) \) chemical species. The reactive sites on the molecules calculated by the dual descriptor \( \Delta f (r) \), which is the difference between the electrophilic and nucleophilic sites by
Fig. 11. NCI isosurface plot (0.7 a.u) of a) Neu5AcClQ^+ and b) Neu5AcClQOH^+.

Fig. 12. Dual descriptor of Fukui function for a) Neu5Ac, b) ClQ^+ and c) ClQOH^+.  

Eq. (4) [49]:
\[
\Delta f(r) = f^+(r) - f^-(r)
\]
for example, when \( \Delta f(r) > 0 \) the site is prone to nucleophilic attack and if \( \Delta f(r) < 0 \), the site is preferred for electrophilic attack.

Fig. 12 shows the dual descriptor graphical representation for Neu5Ac, ClQ^+, and ClQOH^+ and calculated Fukui parameters such as \( f^+(r) \), \( f^-(r) \), and \( \Delta f(r) \) are tabulated in Table S1-S3. In Fig. 12a, positive sites (green color) such as O_{16} and O_{21} are prone to nucleophilic attack through the electrophilic sites on both ClQ^+ and ClQOH^+ (Fig. 12a and b). The electrophilic sites in ClQ^+ (-N_{10}-H_{39}) form hydrogen bond with O_{21} (Fig. 6). On the other hand, the strong electrophilic nature on ClQOH^+ (-N_{10}-H_{30}) facilitates the proton transfer to the O_{10} nucleophilic site (Fig. 7).

4. Conclusion

Molecular recognition of sialic acid (Neu5Ac) with Chloroquine (ClQ) and hydroxychloroquine (ClQOH) were investigated both in gas phase and water using DFT method and B3LYP/6-311++g(d,p) level of theory. The binding of neutral, monoprotonated, and diprotonated forms of ClQ and ClQOH with Neu5Ac were explored to simulate the pH effect on the binding process. The lower band gap of the monoprotonated forms ClQ^+ and ClQOH^+ facilitates the molecular recognition to the Neu5Ac receptor in the gas phase as well as water. In addition, the corresponding Neu5Ac-ClQ^+ and Neu5Ac-ClQOH^+ adducts reveal higher stabilization energies. Molecular Neu5AcClQs and Neu5AcClQOHs stabilized by hydrogen bonding and vdW forces. In addition, the monoprotonated Neu5AcClQOH^+ structure show significant stabilization through the proton transfer process. These results give insight to the molecular mechanism between the cellular receptor ACE2 containing sialic acid with ClQ and ClQOH, which help for future COVID-19 inhibitors research.

Authorship contribution

Tariq Altalhi, Khaled Alswat: Design the idea and perform calculations.
Mohamed M. Ibrahim, Walaa F. Alsanie: Data analysis, interpretation of data.
Ali Aldalbahi: Data analysis, interpretation of data, and help in drafting the manuscript.
Tariq Altalhi, Khaled Alswat, Hamdy S. El-Sheshtawy: Design the idea, perform calculations, Drafting the manuscript and Approval of the version of the manuscript to be published.
Declaration of Competing Interest

Conflict of interest: the authors declare no conflict of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2020.129459.

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