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5-((1H-imidazol-1-yl)methyl)quinolin-8-ol as potential antiviral SARS-CoV-2 candidate: Synthesis, crystal structure, Hirshfeld surface analysis, DFT and molecular docking studies

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**A B S T R A C T**

A potential new drug to treat SARS-CoV-2 infections and chloroquine analogue, 5-((1H-imidazol-1-yl)methyl)quinolin-8-ol (DD1) has been here synthesized and characterized by FT-IR, 1H-NMR, 13C-NMR, ultraviolet-visible, ESI-MS and single-crystal X-ray diffraction. DD1 was optimized in gas phase, aqueous and DMSO solutions using hybrid B3LYP/6-311++G(d,p) method. Comparisons between experimental and theoretical infrared spectra, 1H and 13C NMR chemical shifts and electronic spectrum in DMSO solution evidence good concordances. Higher solvation energy was observed in aqueous solution than in DMSO, showing in aqueous solution a higher value than antiviral brincidofovir and chloroquine. On Bond orders, atomic charges and topological studies suggest that imidazole ring play a very important role in the properties of DD1. NBO and AIM analyses support the intra-molecular O15-H16•••N17 bonds of DD1 in the three media. Low gap value supports the higher reactivity of DD1 than chloroquine justified by the higher electrophilicity and low nucleophilicity. Complete vibrational assignments of DD1 in gas phase and aqueous solution are reported together with the scaled force constants. In addition, better intermolecular interactions were observed by Hirshfeld surface analysis. Finally, the molecular docking mechanism between DD1 ligand and COVID-19/6WCF and COVID-19/6Y84 receptors were studied to explore the binding modes of these compounds at the active sites. Molecular docking results have shown that the DD1 molecule can be considered as a potential agent against COVID-19/6Y84-W6CF receptors.

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1. Introduction

Quinoline and its derivatives have always attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties [1-6]. Literature survey revealed that quinoline derivatives had shown potency as antiviral agents against several viruses such as human immunodeficiency virus, Zika virus, H1N1 influenza virus, Hepatitis C virus, dengue virus, vaccinia virus and respiratory syncytial virus [7-13]. On the other hand, several authors report the antiviral potential of chloroquine as a
therapeutic option against COVID-19, this quinoline derivative presented an EC_{50} of 113 μM in vitro and it caused a negative conversion of the virus in more than 100 patients who participated in multicenter clinical trials conducted in China (in vivo) [14,15]. In the in vitro study recently carried out by Liu et al. [16] have shown that chloroquine and hydroxychloroquine prevent the virus from entering the cell and block the transport of the virus between cell organelles at the later cellular stages of SARS-CoV-2 infection. However, chloroquine has been shown to have higher efficacy [16]. On the other hand, hydroxychloroquine (Fig. 1) has been demonstrated to have an anti-SARS-CoV activity in vitro [17]. A clinical trial using hydroxychloroquine has been conducted in patients infected with SARS-CoV-2. The first results show a significant reduction in viral carriage and the use of hydroxychloroquine added to Azithromycin was significantly more efficient for virus elimination [18].

In view of the therapeutic properties of quinoline derivatives, the investigation of their molecular geometric structure, spectroscopic and electronic properties are fundamental to know the influence of different groups on structures in order to discover the relationship of these groups with their biological properties. In this context, DFT calculations have become a tool very reliable in predicting properties of molecules with great precision [19-25].

Since the quinoline derivatives have shown high potential for the development of new antiviral drugs, herein, we have designed novel 8-hydroxyquinoline derivative i.e, 5-((1H-imidazol-1-yl)methyl)quinolin-8-ol (DD1) (Fig. 1).

**Scheme 1**

This new 8-hydroxyquinoline derivative was synthesized and characterized by using FT-IR, UV-visible, 1H- and 13C-NMR, ESI-MS and single-crystal X-ray diffraction. Then, theoretical B3LYP/6-311++G** calculations were performed to explore its structural, electronic, topological and vibrational properties in gas phase and aqueous and DMSO solutions [26,27]. Thus, with the optimized structures in the different media additional calculations by using the same level of theory were carried out to calculate atomic charges, stabilization energies, bond orders, molecular electrostatic potentials, vibrational frequencies, 1H and 13C NMR chemical shifts and Hirshfeld surface analysis. Due to the importance of this derivative, calculations of frontier orbitals also were performed in order to predict the reactivities and behaviours of DD1 in the different studied media. Finally, the molecular docking mechanism between DD1 ligand and COVID-19/6WCF and COVID-19/6Y84 receptors were studied to explore the binding modes of these compounds at the active sites.

**2. Experimental section**

**2.1. General methods**

All organic solvents were purchased from commercial sources and used as received or dried using standard procedures; all chemicals were purchased from Aldrich, Merck or Alfa Aesar and used without further purification. Analytical thin layer chromatographies (TLC) have been performed on pre-coated silica gel plates (Kieselgel 6 F_{254}, Merck, Germany), and chromatograms were visualized by UV-light irradiation. NMR spectroscopies were recorded in dry deuterated DMSO on a Bruker AC spectrometer at 300 MHz for 1H NMR and 75 MHz for 13C NMR; δ is expressed in ppm related to TMS (0 ppm) as internal standard. Splitting patterns are designated as follow: s (singlet), d (doublet), t (triplet), m (multiplet). Coupling constants (J values) are listed in Hertz (Hz). Mass spectra were obtained using an API 3200 LC/MS/MS system equipped with an ESI source and the samples were diluted in methanol.

**2.2. Synthesis**

An equimolar mixture of the 5-(chloromethyl) quinolin-8-ol hydrochloride (0.57 g, 2.5 mmol), parafomaldehyde (0.075 g, 2.5 mmol) and 1H-imidazole (0.17 g, 2.5 mmol) in EtOH (30 mL) was refluxed for 4-5 h. After cooling, the solvent was evaporated under vacuum and the residue was purified through silica gel column chromatography using hexane/ethyl acetate (ratio 5:5). Green single crystals were obtained by slow evaporation at room temperature.

5-((1H-imidazol-1-yl)methyl)quinolin-8-ol (DD1). Yield = 35%; mp = 184-186°C; 1H-NMR (300 MHz, DMSO-d_{6}, δ(ppm)): 5.56 (s, 2H, CH_{2}), 6.84 (d, J=2Hz, 1H, H4-imidazole), 7.05 (d, J=4Hz, 1H, H7- quinoline), 7.10 (d, J=2Hz, 1H, H4-imidazole), 7.36 (d, J=5Hz, 1H, H-6 quinoline), 7.58 (t, J=8.0Hz, J=4Hz, H-3 quinoline), 7.75 (s, 1H, H2-imidazole), 8.53 (dd, J=8Hz, J=2Hz, H-4 quinoline) 8.85
(dd, J=78Hz, J=2Hz, 1H, H-2 quinoline), 9.93 (s, 1H, OH). $^{13}$C NMR spectrum (75 MHz, DMSO-d$_{6}$) 6 ppm: 46.88, 111.01, 119.89, 122.59, 123.55, 127.06, 128.91, 132.55, 137.77, 139.13, 148.45, 154.01. ESL-MS: m/z = 226.1 [M+H]$^+$, 248.4 [M+Na]$^+$.

2.3. X-ray analysis

The X-ray intensity data for DD1 were collected at 296 K on a STOE IPDS 2 dифрактометр equipped with an X-ray generator operating at 50 kV and 1 mA, using Mo-Kα radiation of wavelength 1.54178 Å. The hemisphere of data was processed using SAINT [28]. The 3D structure was solved by direct methods and refined by full-matrix least squares method on SHELXL program [29,30]. All the non-hydrogen atoms were revealed in the first difference Fourier map and were refined with isotropic displacement parameters. At the end of the refinement, the final difference Fourier map showed no peaks of chemical significance and the final residual was 0.0641. The molecular and packing diagrams were generated using DIAMOND [31].

2.4. Computational details

The theoretical initial structure of DD1 was taken from the CIF file determined in this work by X-ray diffraction. Then, the optimizations were performed in gas phase and aprotic and DMSO solutions by using the functional hybrid B3LYP and the 6-311+G** basis set with the Revision A.02 of Gaussian 09 program [26,27,32]. In this type of molecule the used method performs the better correlations in geometries and frequencies, as was observed by us for other species [19-22]. The integral equation formalism variant polarised continuum model (IEPPCM) method and the solvation model were used for the optimizations in solution by using the same level of theory [33-35]. Atomic charges and topological properties were computed with natural bond orbital (NBO) and atoms in molecules (AIM) calculations [36-38] while the GaussView program was employed to graphic the mapped molecular electrostatic potentials (MEP) obtained from the Merz-Kollman (MK) charges [39,40]. In the vibrational study, normal internal coordinates and transferable scaling factors were used to calculate the harmonic force fields in the different media with the scaled quantum mechanical force field (SQMFF) methodology and the Molvib program [41-43]. In the assignments only those potential energy distribution (PED) contributions $\geq 10\%$ were considered while the correlations in the Raman spectra were improved transforming the predicted spectra in activities to intensities, as suggested in the literature [44,45]. The $^1$H- and $^{13}$C-NMR spectra in aqueous and DMSO solutions were predicted with the Gaussian-Independent Atomic Orbital (GIAO) method [46] with the hybrid B3LYP/6-311+G** method while the electronic spectra at the same level of theory were also predicted by using Time-dependent DFT calculations (TD-DFT) and the Gaussian 09 program [32]. The Moldaw program was used to calculate the volumes variations that experiment DD1 in aqueous and DMSO solutions [47]. The gap values and the chemical potential ($\mu$), electronenegativity ($\chi$), global hardness ($\eta$), global softness ($S$), global electrophilicity index ($\omega$) and nucleophilicity indexes ($E$) descriptors were calculated from the frontier orbitals with the same level of theory and by using known equations [19-22]. In this new derivative is useful to predict the reactivities and behaviours in the different media taking into account the presence of donor (OH) and acceptors (O and N) groups in the structure of DD1 [48,49]. The molecular docking mechanism between DD1 ligand and COVID-19/6WCF and COVID-19/6Y84 receptors were studied by using AutoDock Vina free software program [50].

3. Results and discussion

3.1. X-ray crystal structure description

The details of the X-ray crystal data and the structure solution as well as the refinement of the title compounds are given in Table 1. Supplementary data are deposited at CCDC under deposition numbers 2005089 for DD1. The title compounds crystallized in the monoclinic system. The experimental molecular structure of compound DD1 is illustrated in Fig. 2.

In the title molecule, the phenyl ring (C4–C9) and pyridine ring (N1/C1/C2/C3/C4/C9) are almost planar, making a dihedral angle of 1.805 (1°); the imidazole ring (N2/C11/C12/N3/C13) is twisted with respect to phenyl ring (C4–C9) with a dihedral angle of 65.233 (1°); and the dihedral angle between imidazole and pyridine rings is 66.968 (1°).

For DD1, the torsion angles are, 70.60 (1°) in C11–N2–C10–C5, -110.07 (1°) in C13–N2–C10–C5, 89.30 (1°) in C6–C5–C10–N2, -93.01 (1°) in C4–C5–C10–N2. In the title compound, molecules are linked by O–H$^+$⋯$\equiv$N hydrogen bonds (Fig. 3 and Table 2).

3.2. Molecular Geometric Structures in different media

The hybrid B3LYP/6-311++G** method has optimized the structures of 5-(1H-imidazol-1-yl)methylquinolin-8-ol (DD1) in all media with $C_1$ symmetries where the structure in gas phase compared with the corresponding experimental determined by X-ray diffraction together with the definitions of rings can be seen in Fig. 4. R1 corresponds to pyridine ring, R2 to phenyl ring containing the OH group while the imidazol ring is defined as R3. In Table 3 are presented total energies uncorrected and corrected by zero point vibrational energy (ZPVE), dipole moments and volumes of DD1 in gas phase and aqueous and DMSO solutions by using the B3LYP/6-311++G(d,p) Method. The three calculations evidence a higher stability of structure in gas phase while in aqueous and DMSO solutions the energy values increase notably being slightly less stable in water than DMSO solvent. Perhaps, the higher dipole moment and volume values of DD1 in water justify its lower stability in this medium. In both solvents there is a contraction in the volume when dissolving is performed but, the value is higher in DMSO solution probably due to its higher stability and low dissolution (-1.6 Å$^3$). Thus, the solvent effect can be observed in graphics of orientations and directions of dipole moment vectors because the magnitude is higher in water (Figure S1).

Due to the difference observed in the properties of DD1 in both solvents it is necessary to calculate the solvation energies in the two solvents. Hence, the corrected and uncorrected solvation energies in both solvents calculated from the energies ZPVE can be seen in Table 4.

The results shown in Table 4 have evidenced most negative solvation energy of DD1 in water, as expected because this new derivative is most stable in DMSO. Hence, the $\Delta G_s$ value for the water was obtained from the difference between $\Delta G_{un}$ and $\Delta G_{ne}$, that is, -471.09 - 15.13 = -486.22 kJ/mol. In the same way, in DMSO, the values are: -457.71 - (-7.73) = -449.98 kJ/mol. Note that the total non-electrostatic terms ($\Delta G_{ne}$) present different signs in both solvents, thus, in water that term is positive while in DMSO it has a negative value. The high solvation energy values of DD1 in both media suggest that the acceptors groups (N and O) probably are protonated and charged because previous studies on some antiviral, antihistaminic and alkaloids species have evidenced that in aqueous solution the forms hydrated or cationic present a higher value as compared with the neutral free base or hydrochloride species [51-59], as can be observed in Table S1. If now the ($\Delta G_s$) values of DD1 in aqueous solution are compared with reported
Table 1
Crystal data, data collection and structure refinement details for DD1.

| Crystal data                  | C_{13}H_{11}N_{3}O |
|-------------------------------|---------------------|
| Chemical formula              |                     |
| Mr                            | 225.25              |
| Crystal system, space group   | Monoclinic, P2_{1}/n |
| Temperature (K)               | 296                 |
| a, b, c (Å)                   | 10.2882 (5), 9.7521 (6), 11.0496 (5) |
| β (°)                         | 104.134 (4)         |
| V (Å³)                        | 1075.06 (10)        |
| Z                             | 4                   |
| Radiation type                | Mo Kα               |
| μ (mm⁻¹)                      | 0.09                |
| Crystal size (mm)             | 0.78 × 0.60 × 0.49  |
| Data collection               | STOE IPDS 2         |
| Diffractometer                | Integration (X-RED32; Stoe & Cie, 2002) |
| No. of measured, independent and observed [I > 2σ(I)] reflections | 11136, 3202, 2026 |
| R_{int} (sin θ/λ)_{max} (Å⁻¹) | 0.710              |
| Refinement                    |                     |
| R(F² > 2σ(F²)), wR(F²), S     | 0.042, 0.111, 1.00  |
| No. of reflections            | 3202                |
| No. of parameters             | 155                 |
| H-atom treatment              | H-atom parameters constrained |
| Δρ_{max}, Δρ_{min} (e Å⁻³)    | 0.17, -0.14         |

Fig. 2. The molecular structure (ORTEP) of the compounds DD1.

Fig. 3. A view of the crystal packing of compound DD1 with O—H···N and C—H···N hydrogen bonds.

For antiviral species in aqueous solution from Table S2 [60-65] we observed that DD1 has the lowest (ΔG_{c}) value than the antiviral agents, perhaps due to the three rings present in its structure because the number of acceptors and donors is less than the other ones. From previous studies, we observed that the differences in the solvation energies with another smaller basis set do not present greater differences with those calculated with a higher level of theory [22,61,65].

Table 5 show comparisons of calculated geometrical parameters of 5-((1H-imidazol-1-yl)methyl)quinolin-8-ol (DD1) in gas phase and aqueous and DMSO solutions with the corresponding experimental determined by X-ray diffraction by using root-mean-square
deviation (RMSD) values. These calculations were performed at the same level of theory.

The results shown in Table 5 evidence reasonable correlations in bond lengths (0.039-0.037 Å) and angles (1.1-1.0 °) while higher RMSD values are predicted for the dihedral angles with values between 136.9 and 15 °. Some parameters for DD1 in the three media are overestimated such as, the bond O15-H16 lengths which are longer in the three media than the experimental one probably due to that the calculations show an intra-molecular O-H•••N bond, observing the higher value in DMSO solution, as can be seen in Figure S2. On the contrary, the calculations underestimated the C9-O15-H16 angles showing values between 106.0 and 104.9 ° different from the experimental one of 109.5 °. Here, the contractions of volumes in both solvents are evident compared with the value in gas phase. Note that this angle is higher in water, as expected because the hydration is higher in water due to its higher solvation energy value. The dihedral H16-O15-C9-C4 and H16-O15-C9-C11 angles show interesting results in solution because the first one has negative sign in DMSO solution while the second
one shows negative sign in water and in gas phase. On the other hand, the dihedral O15-C9-C11-H13 angles in both solvents present negative values different from the experimental one with positive sign. Hence, the high RMSD values of dihedral angles reveal higher changes in water than DMSO solution, as expected because this new derivative presents higher solvation energy in aqueous solution.

3.3. Atomic charges, molecular electrostatic potentials and bond orders

As was above mentioned, the high solvation energy values of DD1 in both media could be attributed to that the acceptors (N and O) and donor (OH) groups are protonated and charged and, for these reasons, the calculations related to involved charges on the atoms of those groups are important for this new species as drug candidate [48,49]. Thus, three types of atoms charges, Merz-Kollman (MK), Mulliken and natural population analysis (NPA) charges were calculated on the O15, H16, N17, N21 and N28 atoms of DD1 in gas phase and aqueous and DMSO solutions by using the B3LYP/6-311+G** method [36,39]. These results are summarized in Table S3 while comparisons among them can be observed in Figure S3. Analyzing the MK charges it is observed the same behaviours in the three media with practically the same values and, where the N21 atoms have positive signs while on the N17 and N28 atoms that belong to pyridine and imidazole rings, respectively are observed negative signs. These high negative MK charges observed on N17 and N28 could indicate the formation of H bonds in these sites. However, the Mulliken charges show similar behaviours than the MK ones but the Mulliken charges on the N21 atoms have less positive values and slightly different in the three media. Note that on the N17 and N28 atoms are predicted different Mulliken charges, a resulted different from the MK charges. On the other hand, on the three N atoms are predicted negative NPA charges presenting on the N21 atom in water a less negative value while the most negative values are observed on this same atom in the other two media.

In Table S4 are shown the molecular electrostatic potentials (MEP) and bond orders (BO), expressed as Wiberg indexes for DD1 in gas phase and aqueous and DMSO solutions by using B3LYP/6-311+G** calculations. Regarding first the MEP values, there are not significant differences in the values on those five considered atoms of DD1 in the three media and, only the expected tendency in the values due to the electronegativities values are found, that is, O > N > H. But the higher MEP value is observed on N28, as compared with N17 and N21. When the mapped surface for DD1 in gas phase by using the B3LYP/6-311+G** method is graphed from the GaussView program in Figure S4 [40] the different colorations show clearly the nucleophilic and electrophilic regions that presents DD1. Thus, the region on N28 shows higher electronic density and strong red colour indicating nucleophilic sites while on the O15 and N17 weak orange colours are observed and, as a consequence, these places are weak nucleophilic sites. The strong blue colours is observed on the H16 linked to O15 of OH group. This region is a strong electrophilic site because the H16 is the most labile H atom than the other ones. The aromatic H atoms of pyridine, phenyl and imidazole rings shows ligh blue colours due to that these sites are weak electrophilic regions.

When the bond orders (BO), expressed as Wiberg indexes for DD1 in gas phase and aqueous and DMSO solutions are analyzed from Table S4 and Figure S5, it is observed a low BO value for the H16 atom because this atoms is the most labile while the N21 atom is most strongly linked in DD1 in water than in gas phase and DMSO solution. Then, the BO values for the N17 and N28 atoms are practically the same in the three media. These parameters together with the NPA charges show that the N21 atom of imidazole ring play an important role in the properties of DD1 in the three media.

3.4. NBO and AIM studies

The NBO program allows examining all possible interactions between ‘filled’ (donor) Lewis-type NBOs and ‘empty’ (acceptor) non-Lewis NBOs, and estimating their energetic importance by 2nd-order perturbation theory Analysis of Fock Matrix in NBO Basis [36]. These energies values for DD1 in gas phase and aqueous and DMSO solutions were calculated by using the functional hybrid B3LYP method and two 6-311+G** and 6-31G* basis sets which are presented in Table S5. Here, when the calculations were performed with the higher basis set only was obtained for DD1 in water while for DD1 in gas phase and in DMSO solution the energies were not obtained because in each medium appear a bond orbital with an occupancy of 2.11250 electrons in gas phase while in DMSO solution the number was 2.10906 electrons. However, when the calculations were performed with the 6-31G* basis set the values of energy were obtained in the three media. Fortunately, when we compare the energy values for water with both sets of bases (7015.67 and 6908.62 kJ/mol for 6-31G* and 6-311+G** basis sets, respectively), few differences between them were found, indicating that little influence has the size of the base set on the energy values. For DD1 in the three media are observed six different interactions which are, π→π*, n→σ*, σ→LP, LP→LP, LP→π* and π→π*. The higher energy values are observed in the π→π*, LP→LP* and π→π* transitions carried out from bonding C-C or C-N orbitals to antibonding orbitals and from lone pairs of O and N atoms to C=C or C-N and to lone pairs of H16 atom. These analyses support clearly the presence of intra-molecular O15-H16•••N17 bonds of DD1 in the three media. A very important result is the high energy values of DD1 in gas phase and DMSO solution and the low value in water, evidencing that in aqueous solution is most unstable DD1 due to its higher solvation energy. The presence of different types of interactions were also studied with the Bader’s theory of atoms in molecules (AIM) because this theory use the topological properties to calculate the electron density, ρ(r), the Laplacian values, ∇2ρ(r), the eigenvalues (λ1, λ2, λ3) of the Hessian matrix and, the |λ1|/|λ3| ratio in the bond critical points (BCPs) and ring critical points (RCPs) from the AIM 2000 program [37,38]. Hence, ionic or highly polar covalent interactions or hydrogen bonds interactions are easily predicted when λ1/λ3 < 1 and ∇2ρ(r) > 0 (closed-shell interaction). The resulted of these analyses for DD1 in gas phase and aqueous and DMSO solutions in the BCPs and Ring RCPs by using B3LYP/6-311+G** calculations can be seen in Table S6. Whereas in Figure S6 is shown the molecular graphic only for DD1 in gas phase showing the intra-molecular O15-H16•••N17 interaction. The same interaction is also observed in gas phase and in DMSO solution. The new RCP is named RCPN1 while RCP1, RCP2 and RCP3 correspond to the RCP of pyridine (R1), phenyl (R2) and imidazole (R3) rings. Table S6 shows that the distance between the H16 and N17 atoms that forming those intra-molecular bonds is higher in water than the other ones, as expected because the permittivity of water is higher in this medium (78.355) than the corresponding to DMSO (46.826) and gas (vacuum). Higher parameters are observed in DMSO and lower in water confirming that the stability is higher in DMSO because DD1 has higher solvation energy in water.

3.5. Frontier orbitals and quantum chemical descriptors

Previous studies performed for DD1 in the different media have evidenced interesting properties for this new quinoline derivative and, probably its high solvation energy value in aqueous solution could support its use as antiviral drug candidate. For these reasons,
calculations of frontier orbital, gap values and chemical potential ($\mu$), electronegativity ($\chi$), global hardness ($\eta$), global softness ($S$), global electrophilicity index ($\omega$) and global nucleophilicity index ($E$) descriptors are very important to predict reactivities and behaviours of DD1 in the three studied media [19-22,51,60-65]. Table S7 shows those parameters for DD1 in gas phase and aqeous and DMSO solution by using the B3LYP/6-311++G** method compared with the hydrochloride form of antiviral adamantadine in water and with both $S$ and $R$ forms of chloroquine in water by using the same level of theory. The differences between HOMO and LUMO, named gap, shows lower values in DD1 in the three media and, hence, a higher reactivity is expected for DD1 and, in particular, in DMSO solution while the $R$ form of chloroquine is the less reactive than the other ones. A higher global electrophilicity index ($\omega$) and a lower global nucleophilicity index ($E$) predicted for DD1 in DMSO could justify its higher reactivity in this medium. Comparisons of these parameters with reported for antiviral agents in the same medium and with the same basis set suggest that DD1 could be a very good antiviral drug candidate.

3.6. Vibrational study

The experimental infrared spectra of the title compound DD1 in the solid state was recorded using reflectance (ATR) mode and its comparison with the corresponding predicted in the gas phase and aqueous and DMSO solutions by using the B3LYP/6-311++G** method are given in Fig. 5. The predicted Raman spectra of DD1 in the three media can be seen in Fig. 6. Here, the theoretical Raman spectra were corrected from activities to intensities by using recommended equations [44,45]. The optimized structures in the three media present $C_1$ symmetries and 28 atoms, hence, for this species are expected 78 vibration normal modes. All vibration modes present activity in the infrared and Raman spectra. The scaled quantum mechanical force field (SQMFF) methodology and the Molvib program were used, together with the normal inter-

Fig. 5. Experimental infrared spectra of 5-(1H-imidazol-1-yl)(methyl)quinolin-l-ol (DD1) in the solid phase compared with the predicted in gas phase and aqueous and DMSO solution by using the hybrid B3LYP/6-311++G** method.
Table 6

| Exp | DD1 | GAS | PCM | IR | Int | SQM | Assignments | PCM | SQM | Assignments |
|-----|-----|-----|-----|----|-----|-----|-------------|-----|-----|-------------|
| 3490vw | 113.8 | 3480 | νO15-H16 | 3409 | νO15-H16 |
| 3168w | 2.5 | 3125 | νC22-H25 | 3162 | νC22-H25 |
| 3120sh | 1.1 | 3115 | νC23-H26 | 3157 | νC23-H26 |
| 3100sh | 4.6 | 3101 | νC24-H27 | 3133 | νC24-H27 |
| 3092w | 7.3 | 3068 | νC2-H7 | 3100 | νC1-H6 |
| 3080sh | 4.6 | 3066 | νC11-H13 | 3091 | νC11-H13 |
| 3044vw | 5.0 | 3054 | νC1-H6 | 3087 | νC2-H7 |
| 10.7 | 3032 | νC12-H14 | 3070 | νC12-H14 |
| 2985w | 16.7 | 3024 | νC5-H10 | 3066 | νC5-H10 |
| 2960w | 10.0 | 2943 | νC13-H14 | 3004 | νC13-H14 |
| 2913w | 30.5 | 2911 | νC15-H15 | 2962 | νC15-H15 |
| 1687w | 14.4 | 1610 | νC9-C11 | 1624 | νC9-C11, νC8-C12 |
| 1616w | 6.1 | 1582 | νC1-C2, νC8-C12 | 1597 | νC1-C2 |
| 1568m | 37.9 | 1563 | νC5-N17 | 1578 | νC5-N17 |
| 1500s | 134.8 | 1488 | νC1-C5 | 1509 | νC23-N23 |
| 0.3 | 1481 | νC22-C24 | 1502 | νC22-C24 |
| 1472s | 60.0 | 1474 | νC23-N28, βC/H26 | 1500 | νC1-C5, βC/H16 |
| 1448m | 104.9 | 1457 | νC4-C9 | 1465 | βC/H5-H10, νC4-C9 |
| 1436sh | 24.7 | 1435 | δC/H2 | 1454 | δC/H2 |
| 1409m | 14.5 | 1407 | βC/H10 | 1421 | wagCH3, βC/H5-H10 |
| 15.0 | 1394 | βC-H2, βC-H7, νC3-C8 | 1412 | wagCH3 |
| 1388m | 24.4 | 1387 | wagCH2 | 1409 | βC-H7 |
| 1368w | 49.6 | 1356 | νC3-C4, νC8-C12 | 1367 | νC3-C4 |
| 1345m | 26.8 | 1332 | νC3-C4 | 1343 | νC5-N17, νC3-C4 |
| 1333sh | 2.5 | 1325 | νC23-N28 | 1333 | νC23-N28, νC23-N21 |
| 1297sh | 20.0 | 1296 | νC23-N21 | 1330 | νC23-N28, νC23-N21 |
| 1269s | 68.9 | 1266 | βRr(A2) | 1278 | βC4-H27 |
| 1269s | 80.2 | 1264 | βC4-C24, H27 | 1265 | βRr(A2) |
| 1237sh | 10.7 | 1245 | βC12-C14 | 1259 | βC12-C14 |
| 1237sh | 121.6 | 1121 | νC8-C18 | 1226 | βC23-H26, νC18-N21 |
| 1217sh | 61.9 | 1121 | νC18-N21 | 1214 | νC2-C3, νC3-C8, νC4-N17 |
| 1205sh | 34.2 | 1191 | νC13-H14 | 1204 | νC13-H14 |
| 1181m | 11.0 | 1180 | δO15-H16, νC2-C3 | 1172 | δO15-H16 |
| 1150m | 3.4 | 1143 | βC11-H13 | 1149 | βC11-H13 |
| 1142sh | 2.8 | 1137 | βC1-H6, νC11-C12, νC8-C18 | 1137 | νC11-C12, βC11-H13, νC9-O15, νC8-C18 |
| 1102sh | 22.9 | 1100 | νC24-N28 | 1101 | νC24-N28 |
| 1074s | 2.5 | 1068 | βRr(A1) | 1067 | βC22-H25 |
| 1054sh | 40.3 | 1058 | βC22-C25 | 1062 | βRr(A1) |
| 1030m | 1.5 | 1044 | νC1-C5, βRr(A1) | 1056 | νC1-C5 |
| 1010sh | 5.0 | 1017 | νC22-N21 | 1019 | βRr(A3), νC22-N21 |
| 18.3 | 1801 | νC17 | 1005 | νC1-C5 |
| 986sh | 0.4 | 989 | νC1-H6 | 999 | νC1-H6 |
| 951sh | 1.5 | 952 | νC5-H10, νC2-H7 | 967 | νC5-H10 |
| 927sh | 0.8 | 945 | νC12-H14 | 953 | νC12-H14 |
| 911sh | 2.9 | 909 | βRr(A3) | 912 | βRr(A3) |
| 871sh | 8.6 | 882 | τCH2 | 891 | τCH2 |
| 859sh | 1.9 | 854 | νC24-H27 | 850 | νC11-H13 |
| 843sh | 21.6 | 841 | νC11-H13 | 842 | νC24-H27 |
| 823s | 4.6 | 827 | βRr(A2) | 827 | βC23-H26 |
| 823s | 25.5 | 814 | νC23-H26 | 826 | βRr(A1) |
| 791s | 26.6 | 805 | τRr(A1), νC2-H7 | 816 | νC2-H7 |
| 752sh | 20.9 | 779 | τRr(A2) | 778 | τRr(A2), τRr(A1) |
| 728sh | 3.3 | 765 | τRr(A1), τRr(A2) | 760 | τRr(A1), τRr(A2) |
| 728sh | 10.1 | 725 | τRr(A1), τC18-N21 | 732 | τC22-H25 |
| 696s | 34.4 | 715 | νC22-H25 | 728 | τRr(A1), νC18-N21 |
| 696s | 25.6 | 696 | βRr(A1) | 695 | βRr(A1) |
| 660s | 15.6 | 651 | τRr(A3) | 653 | τRr(A3) |
| 640m | 33.8 | 632 | τRr(A1) | 629 | τRr(A1), τRr(A2) |
| 620m | 65.1 | 603 | τRr(A3) | 602 | τRr(A3) |
| 65.2 | 593 | νC9-K15 | 595 | νC9-O15 |
| 577w | 1.3 | 570 | βRr(A1), νC9-O15 | 567 | βRr(A1), νC9-O15 |
| 7.7 | 569 | τO15-C9 | 535 | βRr(A1) |
| 545sh | 0.6 | 537 | βRr(A2) | 504 | βRr(A2) |
| 17.6 | 507 | βRr(A2) | 492 | τO15-C9 |
| 493m | 0.2 | 492 | βRr(A2) | 490 | βRr(A2) |
| 465w | 0.2 | 459 | τRr(A2) | 463 | τRr(A2) |

(continued on next page)
Table 6 (continued)

| Exp | DD1b | GAS | SQM | Assignmentsa | PCM | SQMb | Assignmentsa |
|-----|------|-----|-----|-------------|-----|------|-------------|
| 453sh | 1.9 | 413 | rR1(A1) | 413 | rR1(A1) | 413 | rR1(A1) |
| 0.9 | 353 | rR2(A2), rR2(A1) | 360 | rR1(A2), rR2(A1) | | |
| 1.5 | 312 | βN21-C18 | 330 | βN21-C18 | | |
| 3.2 | 280 | γC9-O15 | 277 | βN21-C18, γR2(A2) | | |
| 2.4 | 272 | βR2(A2), βC8-C18 | 269 | γC9-O15 | | |
| 2.2 | 192 | βC8-C18 | 196 | βC8-C18 | | |
| 2.3 | 177 | ButC3-C4, γN21-C18 | 177 | ButC3-C4, γN21-C18 | | |
| 0.1 | 148 | rR2(A2) | 146 | rR1(A2) | | |
| 0.6 | 132 | rR2(A1) | 133 | rR1(A1) | | |
| 1.3 | 50 | γC8-C18, βC8C18N21 | 48 | γC8-C18, βC8C18N21 | | |
| 0.3 | 36 | rC18-N21 | 41 | rC18-N21 | | |
| 2.9 | 33 | rC18-C8 | 25 | rC18-C8 | | |

Abbreviations: ν, stretching; β, deformation in the plane; γ, deformation out of plane; wag, wagging; τ, torsion; ρ, deformation ring; ρw, torsion ring; ρ, rocking; τw, twisting; δ, deformation; a, antisymmetric; s, symmetric; (A1), Ring 1; (A2), Ring 2; (A3), Ring 3; a This work, b Intensities in KM/Mole; c From scaled quantum mechanics force field.

Assignments skeletal groups. The C=N stretching vibration is reported at 1613 cm\(^{-1}\) by Sheeja et al. [72]. Here, the C5=N17 and C23=N28 stretching modes are predicted in gas phase at 1563 and 1474 cm\(^{-1}\) while in solution at 1578 and 1333 cm\(^{-1}\). Note that the C23=N28 stretching mode in solution is predicted coupled with the C23-N21 stretching mode. The aromatic C=C-C stretching vibrations of aromatic ring are very much important and occur in the region 1200-1650 cm\(^{-1}\) [19-22,55-58,60]. In DD1, the IR bands in the range 1687-1457 cm\(^{-1}\) are assigned to C=C stretching mode in aromatic rings while the C=C stretching modes are predicted by SQM calculation between 1367 and 1001 cm\(^{-1}\). Then, these modes are assigned in those regions, as predicted by calculations. Here, the C18-N21 stretching modes in both media are predicted couples with one of torsion modes of pyridine ring between 728 and 725 cm\(^{-1}\), that is, practically in the same region. Hence, we can see that that mode is not influenced by the medium. The assignments of other groups in the 360 and 25 cm\(^{-1}\) region such as, deformations and torsions of three rings were not performed because the infrared spectrum was recorded only until 400 cm\(^{-1}\).

3.7. Force fields

Calculations of harmonic force fields for DD1 in the three media by using the B3LYP/6-311++G** method have allowed to compute the scaled force constants which are very important parameters that explain the forces of different bonds. Thus, these constants are obtained when the harmonic force fields are transformed from Cartesian coordinates to normal internal coordinates with the SQMFF methodology and the Molvib program [41-43]. The results for DD1 in the three media are presented in Table 7. The \(f(vC-H)_{R1}\) force constants corresponding to the C-H bonds of different rings were separate in R1 (pyridine), R2 (contain the OH group) and R3 (imidazole) because they have different behaviours and environments in the different media. Thus, first analyzing the \(f(vO-H)\) force constants we observed that in DMSO solution DD1 present the lower force constant while in gas phase the value is higher. This observation is in agreement with the lower frequency

![Fig. 6. Predicted Raman spectrum of 5-[(1H-imidazol-1- y)methyl]quinolin-8-ol (DD1) in gas phase and aqueous and DMSO solution by using the hybrid B3LYP/6-311++G** method.](image)
predicted for this bond in DMSO (3409 cm⁻¹) while in water the value increase to 3480 cm⁻¹. On the contrary, when the \( f(v-C-O) \) force constants are evaluated we observe that in DMSO solution it has a higher value and, it cannot be explained by the frequencies of stretching modes because in both solutions these modes are coupled. An explanation could be due to higher value of \( f(v-O-H) \) force constant and, hence, to decreasing in the corresponding \( f(v-C-O) \) force constant.

When the \( f(v-C-H)_{23} \) force constants are analyzed, for the ring R3 are observed the higher values in the three media and, these observations are related to the lower \( f(v-C-N)_{23} \) force constants values evidenced for this ring. Moreover, the MEP value for the N28 atom and the NPA and BO predicted for the N21 atom of R3 ring and, in addition, to its higher electron density, this ring R3 play a very important role in the properties of DD1 in the three media. Thus, due to the proximity of CH₂ group to ring R3 the stretching modes are influenced by the medium because in solution are observed higher force constants values than in gas phase. However, the deformations of those groups practically are practically similar in the three media.

### 3.8 Ultraviolet-Visible spectrum

The experimental ultraviolet-visible spectrum of DD1 in DMSO solution recorded between 200 and 400 nm region can be seen in Figure S8 compared with the corresponding predicted in aqueous and DMSO solutions by using Time-dependent DFT calculations (TD-DFT) with the hybrid B3LYP/6-311++G** method. In the experimental spectrum we observed a set of intense bands in the higher wavelengths region where the enveloping line presents a maximum at 238 nm and another less intense and wide band at 328 nm. In the predicted electronic spectrum in aqueous solution are also observed two bands, the most intense at 234.7 and te other one at 344.2 nm while in DMSO the positions of these two bands increase respectively at 236.6 and 346.2 nm. The presence of C≡C, C≡N and lone pairs of N and O atoms justify the presence of those two bands observed in the electronic spectra of DD1 in the three media which are assigned to \( \pi \rightarrow \pi^* \), \( \pi p \rightarrow \pi p^* \) and \( \pi^* \rightarrow \pi^* \) transitions because these present higher energies values, according to NBO calculations.

### 3.9 \(^1\)H- and \(^{13}\)C-NMR spectra analysis

The experimental \(^1\)H- and \(^{13}\)C-NMR spectra of DD1 were obtained by using TMS as an internal standard and DMSO-d₆ as solvent (Figs. S9 and S10). In Tables 8 and 9 are shown the experimental chemical shifts of protons and C atoms compared with the corresponding predicted by using Gauge-Independent Atomic Orbital (GIAO) method [46] with the hybrid B3LYP/6-311++G** method. The \(^1\)H-NMR chemical shifts of H-19 and H-20 protons of the methylene group (CH₂) of DD1 appear as a singlet at 5.56 ppm, respectively. The chemical shifts of H-15 and H-25 protons of quinoline appear as a triplet and doublet at 7.59 and 7.06 ppm. These chemical shifts are relatively well reproduced with deviations less than 0.57-0.47 ppm compared to the observed ones. The chemical shifts of H-27 proton of quinoline appear as a doublet at 7.36 ppm for DD1. The chemical shifts of H-11 and H-23 protons appear as two doubles of doublets at 8.53, 8.85 ppm. The observed chemical shifts of the hydroxy (H-2) proton of DD1 appear as singlet at 9.53 ppm. The chemical shifts of the protons of imidazole ring in DD1 appear as a singlet and two doublets at 7.75, 6.84 and 7.10 ppm. Also, reasonable correlations were found for the C atoms with RMSD values between 5.57 and 5.34 ppm. The \(^{13}\)C-NMR chemical shifts of the C-12 (C-8-CH) of DD1 are observed at 154.01 ppm. The signals observed at 148.54 ppm are attributed to the C-22 carbon (C=O) of the quinoline. The C-10, C-14, C24 and C26 carbon chemical shifts of the title compound occurred in the range of 111.01-132.86 ppm. The signals at 119.89, 128.91 and 139.13 ppm in \(^{13}\)C NMR spectrum of DD1 are clearly assigned for three carbons of imidazole ring. The C-18 carbon chemical shift of the methylene group (CH₂2) of DD1 is obtained at 46.88 ppm.

### 3.10 ESI-MS spectra analysis

The ESI-MS spectra of DD1 show molecular ion peaks with m/z values 226.1. The peaks correspond to the molecular weight [M+H]+ of DD1. The m/z value at 248.4 is assigned to the sodiated molecular ion peak [M+Na]+ for DD1 (Fig. S1). These values are in good agreement with the proposed composition for the title compound.
3.11. Hirshfeld surface analysis

In this section, the Hirshfeld surface analysis of the DD1 molecule were carried out with the help of Crystal Explorer 3.1 program [73]. Thanks to this analysis, the locations of the possible hydrogen bonds in the crystal structure and the packaging model can be easily seen and there are three type color (red, blue and white) in the visualization of intermolecular interactions [74,75]. For analysis, cif* (Crystallographic Information File) of the compounds are used. The $d_{	ext{norm}}$ values of compounds were obtained as -0.6660 to 1.1031 a.u. for DD1. Here, the negative values represent red, positive values represent blue color and $d_{	ext{norm}}$ mapped on Hirshfeld surfaces were shown as in Fig. 7.

In Fig. 7, the dark red points focused on N, O, H atoms, here O–H...N interaction was observed with 1.774 Å, additionally in this figure O–H interaction point was shown.

Secondly, the 2D (two-dimensional) fingerprint plots with their relative contributions to the Hirshfeld surfaces we indicated in Fig. 8a-e for DD1. As seen from the Fig. 8, the most important interactions were determined with H–H (35.9%), C–H/C–H (30.3%), N–H/H–N (19.8%) and O–H/O–O (9%) contributions.

3.12. Molecular Docking Studies

In this section, the molecular docking analysis of 5-((1H-imidazol-1-yl) methyl) quinolin-8-ol (DD1) ligand with COVID-
19/6WCF and COVID-19/6Y84 receptors were performed. For structure-based drug design, the molecular docking is very crucial [76,77]. Here as ligand, DD1 molecule was optimized with B3LYP/6-311++G(d,p) and was recorded PDB-Protein Data Bank format. Later, the two target proteins were determined with the help of literature and PDB structures of receptors were downloaded from the Protein Data Bank [78]. The specific treatment for COVID-19 is not available to date, so by researchers many antiretroviral drugs against COVID-19 were reported and was offered such as ritonavir, lopinavir, oseltamivir, remdesivir, chloroquine and hydroxychloroquine [79]. Since some of these structures are quinoline derivative, we decided to do docking analysis of DD1 that we can recommend against COVID-19. In the receptors water molecules and co-factors were removed. Both ligands and receptors were prepared and recorded as PDBQT formats with Discover Studio Visualizer 4.0 (DSV 4.0) software [80]. The molecular docking computations were performed with AutoDock Vina program [50].

Let’s first look at the interactions between DD1 ligand and the 6Y84 receptor. 6Y84 is the COVID-19 main protease with unliganded active site. SARS-CoV-2 main protease has a vital role in the processing of polyprotein that is translated from viral RNA, and the protease is considered as key for viral survival and growth [81]. The active sites of PDB:6Y84 were determined as ARG298, ASP295, ASP263, THR224, PHE223, GLN127, SER113, LYS97, ARG76, LEU75, GLN74, ASN65, HIS64, MET17, GLY15, PHE8 and MET6 and according to these active residues the grid boxes were taken as centre_x=-8.562, centre_y=1.084, centre_z=5.876, size_x=76, size_y=72, size_z=80, spacing=0.442. For these interactions, the docking results were given in Table 8, also between DD1-6Y84 docking mechanism as 2D and 3D were shown in Fig. 9.

In addition, the positions of DD1 within the receptor (6Y84) were shown in Fig. 10. The best binding was determined with -7.2 (kcal/mol) energy between DD1 ligand and 6Y84 receptor according to the affinity energies with two hydrogen bonding. But one active hydrogen bonding was observed GLN127 active residue and H2 atom with 2.33 Å bond distance as seen Fig. 9. Furthermore, from the Fig. 9 van der Waals, π-cation, π-donor hydrogen bond and π-alkyl interactions could be easily seen. At the last of the tables, the obtained inhibition constants and the number of hydrogen bonding for DD1-6Y84 interactions were given.

Secondly, the molecular docking mechanism between DD1 ligands and the 6WCF receptor was investigated and evaluated. 6WCF is Crystal Structure of ADP ribose phosphatase of NSP3 from SARS-CoV-2 in complex with MES [82]. The active sites of PDB:6WCF were detected as PHE132, ILE131, GLY130, ALA129, ASN72, THR71, SER128, LYS55, ALA52, GLY51, GLY47, GLY46, LYS44, ASN40, and ALA38. As mentioned before, the grid parameters were determined to include the active region as follows: centre_x=4.969, centre_y=8.796, centre_z=-5.972, size_x=62, size_y=84, size_z=42, spacing=0.375. The same grids were used in both ligands and the docking scores were tabulated in Table 9 and additionally between DD1-6WCF docking mechanism were indicated as 2D and 3D in Fig. 11.

Furthermore, the positions of DD1 within the 6WCF receptor were indicated in Fig. 11. As seen from the Table 9, the best binding was determined with -6.2 (kcal/mol) energy between DD1 ligand and 6WCF receptor with two active hydrogen bonding (Fig. 10).

The bond distances between ALA129-N5 and SER128-N6 were determined as 2.35 and 2.70 Å, respectively. Additionally, from the

![Fig. 9. The molecular docking results of the DD1 compound with 6Y84 protein, surfaces around ligand (a) and 2D forms (b).](image)

![Fig. 10. The molecular docking positions of the DD1 compound within 6Y84 protein.](image)
Fig. 11. The molecular docking results of the DD1 compound with 6WCF protein, surfaces around ligand (a) and 2D forms (b).

Fig. 12. The molecular docking positions of DD1 within 6WCF protein.

4. Conclusions

In this work, a new chloroquine analogue, 5-[(1H-imidazol-1-yl)methyl]quinolin-8-ol (DD1) with potential antiviral agent against COVID-19/6Y84-6WCF receptors has been synthesized and characterized by FT-IR, 1H-NMR, 13C-NMR, UV-visible, ESI-MS and single-crystal X-ray diffraction. Good correlations between experimental and theoretical infrared spectra, 1H and 13C NMR chemical shifts and electronic spectrum in DMSO were obtained by using the hybrid B3LYP/6-311+G(d,p) method. Structural, electronic, topological and vibrational properties were performed in gas phase, aqueous and DMSO solutions. Higher solvation energy was observed in aqueous solution than in DMSO showing higher solvation energy in aqueous solution than antiviral brincidofovir and chloroquine. Behaviors of atomic Mulliken, NPA charges and topological properties suggest that imidazole ring play a very important role in the properties of DD1. NBO and AIM analyses support the intra-molecular O15-H16-..-N17 bonds of DD1 in the three media evidencing higher stability in DMSO solution. The low gap values suggest a higher reactivity of DD1 in DMSO solution justified probably by the higher electrophilicity and low nucleophilicity. Comparisons of gap with antiviral agents suggest that DD1 could be a very good antiviral drug candidate. Here, the complete vibrational assignments of DD1 in gas phase and aqueous solution are reported together with the scaled force constants. Hirshfeld surface analysis was performed to observe better intermolecular interactions in the crystal packing of DD1. Finally, molecular docking results have shown that the compound can be considered as a potential agent against COVID-19 / 6Y84-6WCF receptors.

Credit Author Statement

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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.

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Supplementary materials

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