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Synthesis, spectral characterization, crystal structure and computational investigation of 2-formyl-6-methoxy-3-carbethoxy quinoline as potential SARS-CoV inhibitor

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ABSTRACT

The recent COVID-19 outbreak caused by the novel coronavirus SARS-CoV-2 has an immense impact on global health and economy. Although vaccines are being used, urgent need of drugs based on natural products with high efficacy and safety is a pressing priority. Quinoline alkaloids are well known for their therapeutic action against malaria; initially, it was tried against Coronaviruses. It is a basic vital scaffold to design drugs with required biological and pharmacological activities. In this present study, a new quinoline compound was synthesized and characterized by spectroscopy techniques. Crystal structure was established by SCXRD analysis and data is used as an input to perform various computations. Additionally, using state-of-the-art quantum computational techniques, the geometry optimization and calculation of UV–Vis spectrum of 2F6M3CQ were performed at B3LYP/6-311G* level of theory. The optimized molecular geometric parameters as well as UV–Vis spectrum values are found to be in good agreement with their respective experimental results. The visualization of 3-D plots of FMO and MEP indicated the structure and reactivity trends of 2F6M3CQ molecule. Molecular docking methods were utilized to find the drug ability of 2F6M3CQ with M\textsubscript{pro} protein of SARS-CoV-2. There were many intermolecular interactions between M\textsubscript{pro} protein and 2F6M3CQ molecule which lead to good binding energy (\textasciitilde 5.5 kcal/mol) between which was found to be better than the binding energy of chloroquine molecule (\textasciitilde 4.5 kcal/mol) as studied under same docking protocols. Finally, drug likeness and ADME properties of 2F6M3CQ were also analyzed. There is no violation found for RO5 in our 2F6M3CQ compound. ADME analysis shows drug like properties of compound 2F6M3CQ which predicts that it might be a potential candidate for inhibition of SARS-CoV-2.

1. Introduction

The novel human coronavirus disease (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2). These viruses can infect some animals and human beings, SARS-CoV-2 infected human were first reported from Wuhan City, China, in December 2019 \cite{1}. The World Health Organization (WHO) data shows that until the middle of 2022 there were 540 million Covid-19 human infections, including 6.3 million deaths. SARS-CoV-2 enveloped non-segmented, spherical positive RNA genome have 5\textasciitilde cap structure along with the 3\textasciitilde poly tail structure \cite{2,3}. The untranslated region (UTR) of the 5\textasciitilde end genome has multiple steam loop structure for RNA transcription and replication. Similarly, the UTR of 3\textasciitilde end also have RNA structure for replication and synthesis of viral RNA \cite{4}. The non-structural proteins and replications parts are placed in the 5\textasciitilde end of CoV genomes and the structural proteins and open reading frames are present in the 3\textasciitilde end of CoV genomes \cite{5}. Main protease [M\textsubscript{pro}] is a crucial protein in coronavirus, which cleaves the polyproteins during virus replication and is one of the anti-viral target designed for drug development \cite{6-8}.
The crystal structures of M\textsuperscript{Pro} with ligand and unbounded form are already deposited in protein data bank [9]. Anti-viral drugs such as Lopinavir and ritonavir were the first drugs used in clinical trials to treat SARS-CoV-2 targeting M\textsuperscript{Pro} [10]. The antimalarial drugs like chloroquine, hydroxychloroquine have been studied as a potential treatment for COVID-19 [11]. It has quinoline skeleton in its structure and some antimalarial drugs like quinine, mefloquine, and amodiaquine also have the quinoline moiety [12,13].

Remdesivir, is a novel antiviral drug potentially used for the treatment of Ebola and Marburg virus and also other viral infections. In vitro studies showed that it can control SARS-CoV-2 infections effectively with significant reduction in mortality [14]. Umifenovir, Favipiravir, Molnupiravir [15], Nirmatrevir mixed with Ritonavi [16], Ribavirin [17] and Interferon are some of the other antiviral agents approved for treatment of SARS-CoV-2 [18], while some of them might have potential side effects [19]. COVID-19 pandemic has put the global research on a war footing to find an effective drug as well as suitable antiviral therapies [20]. Synthetic organic chemistry provides newer routes of drug development with new molecules for further investigations [21]. The new drugs with required pharmacological quality can be crafted carefully following a step by step synthetic procedures [15].

Quinoline core structure plays an important role in the fight against numerous critical diseases and is also present in various natural products especially cinchona alkaloids [22]. The quinoline nucleus has high impact against the progress of various antibacterial agents, and is used in the form of anti-bacterial drugs like levofloxacin, ciprofloxacin and norfloxacin [23].

This core structure is also present in familiar synthetic anticancer drugs like topotecan and irinotecan [24]. Some quinoline derivatives also have been found to possess antifungal [25], antiviral [26], anthelmintic [27], cardiotonic [28], antineoplastic [29] and anti-inflammatory [30] activity.

On the other hand, computational chemistry tools are becoming more and more realistic owing to the emergence of several new algorithms. The computational tools were recently used in characterization of chemical structures, interactions, chemical properties of molecules and many other similar problem solving tasks. Density functional theory (DFT) is one of the popular computational chemistry techniques to understand the molecular structure and its application, which is growing quickly. It is a successful and promising approach in theoretical estimations such as total energy of the system, atomic charge, electric and magnetic properties, vibrational frequencies, atomization energies, ionization energies, and reaction pathways [31–36].

In the above context our present work is focused on the synthesis of functionalized quinoline from Vilsmeier – Haack heterocyclization of β-anilinocrotonate, followed by oxidation using selenium dioxide. The newly synthesized compound was characterized explicitly by various physiochemical methods like UV, FT-IR, \textsuperscript{1}H NMR, \textsuperscript{13}CNMR and Single Crystal XRD analysis. Apart from analyzing the synthesized compound, the computational calculations (DFT methods) are to be performed to investigate the molecular structure and UV–Visible spectral characterizations of newly synthesized compound. The ligand-protein...
interactions, binding energy and binding modes of the synthesized compound are to be investigated by molecular docking studies through grid base scheme. Besides this, a brief drug likeness will be also predicted using several online servers.

2. Experimental details

2.1. Materials and methods

All the starting compounds and solvents used for synthesis were purchased from Sigma Aldrich and TCI India. They were used as received without any further purification. The IR spectrum of the title compound was recorded by Schimadzu FT IR PC (S) 8201 spectrometer using Nujol mull methods in the frequency region of 400–4000 cm⁻¹.

The UV-Visible-NIR spectrum of 2-formyl-6-methoxy-3-carbethoxy quinoline (2F6M3CQ) was recorded in Jasco UV-Visible-NIR V 670 spectrophotometer in the wavelength range 200–800 nm in methanol medium. Photoluminescence spectrum was recorded in Horiba JobinYvon FluoroLog-3 Modular Spectrofluorometer using methanol as solvent. Single crystal X-ray diffraction parameters were measured by Bruker AXS Kappa APEX II CCD X-ray diffractometer using MoKα radiation of wavelength 0.7107 Å.

3. Synthesis and crystal growth

3.1. Preparation of β-anilinocrotoante

p-Anisidine (0.0813 mol, 10g) and ethyl acetoacetate (0.1374 mol, 17.5 mL) was taken in a beaker and catalytic amount of 1:1 HCl was added. The solution was kept undisturbed for two days. The formed product water was separated and the solution was dried with sodium sulphate and used as such subsequently for the next step.

3.2. Preparation of 6-methoxy-2-methyl-3-carbethoxy quinoline

Dimethylformamide (0.1195 mol, 9.2 mL) and β-anilinocrotoante (0.1173 mol, 24.5 mL) was taken in a two necked round bottom flask, equipped with condenser and cooled at 0 °C. To it, phosphorus oxychloride (0.1195 mol, 11.25 mL) was added dropwise from a dropping funnel with constant stirring for half an hour. The whole of the mixture was heated over a water bath for 4 h. After cooling, the reaction mixture was poured into excess of water and was neutralized by sodium hydrogen carbonate solution. The organic compound was passed on to chloroform and the chloroform layer was separated, washed and dried. Excess chloroform was removed under reduced pressure. The obtained oily substance was activated using silica gel and was column chromatographed using petroleum ether: ethyl acetate (97:3), a yellow solid was obtained (M.P: 73 °C, Yield: 79%).

3.3. Preparation of 2-formyl-6-methoxy-3-carbethoxy quinoline

About 18 mL of 1,4-dioxane along with 1.8 mL water (10%), was added to 0.015 mol of freshly prepared selenium dioxide and the mixture warmed at 45 °C. To the warmed mixture was added 0.01 mol of 2-methyl-3-carbethoxy quinoline in 7 mL of 1,4-dioxane slowly over a period of 15 min and then the whole mixture was refluxed at 110 °C with constant stirring for 1 h whereby the reduced selenium settled down which was filtered off. The 1,4-dioxane was stripped off under reduced pressure and the whole of the mixture was extracted with chloroform and was activated using silica gel. It was column chromatographed over silica gel at (96:4) petroleum ether: ethyl acetate as eluent (white colour powder, M.P:110 °C, Yield: 61%). The solubility of the title compound was studied in various solvents such as methanol, ethanol and ethyl acetate. The study indicated that the title crystal shows a positive solubility temperature gradient in ethanol. Hence ethanol was chosen as growth solvent to grow good quality single crystals. A saturated solution of titled substances in ethanol was prepared and stirred well for about half an hour to dissolve the material completely. The solution was then filtered through a quantitative Whatmann No.41 grade filter paper to get rid-off the suspended impurities totally. The clear filtrate was kept aside unperturbed in a congenial atmosphere for the growth of single crystals. After a normal growth period of 7 days, crystals of the size (0.400 × 0.300 × 0.300 mm) were obtained. The individual crystal was plucked using a needle and washed with petroleum ether then it was dried and packed for further analysis (see Scheme 1).

Scheme 1. Synthesis of 2-formyl-6-methoxy-3-carbethoxy quinoline (2F6M3CQ).
4. Physicochemical characterization

4.1. FT-IR spectral analysis

The IR spectrum of 2F6M3CQ (Fig. S1) shows absorption at 2920 cm\(^{-1}\) due to –CH stretching vibrations of methoxy and carbethoxy groups. The aromatic C–H stretching was observed at 3000 cm\(^{-1}\). The carbonyl stretching frequencies of ester and aldehyde groups appeared at 1710 cm\(^{-1}\) and 1699 cm\(^{-1}\) respectively. Aromatic C–N stretching was observed at 1618 cm\(^{-1}\) while 1461 cm\(^{-1}\) was due to –O–C\(_2\)H\(_5\) stretching vibrations. In the compound there was a strong hydrogen bonding interaction between aldehyde proton and carbonyl group of the ester. As a result of which, the stretching frequency of ester carbonyl underwent a reduction from the expected 1730 cm\(^{-1}\) to 1710 cm\(^{-1}\).

4.2. NMR spectral analysis

In \(^1\)H NMR spectrum (Fig. S2) the C4-CH appeared as singlet at 8.44 ppm, the proton on C8-CH appeared as doublet at 8.20 ppm (\(J = 9.28\) Hz), the C7-CH proton appeared as doublet at 7.54 ppm (\(J = 9.28\) Hz, 1.2 Hz), the C5-CH proton appeared as singlet of doublet at 7.17 ppm (\(J = 1.28\) Hz), the two protons at C3-3′-CH\(_2\) appeared as quartet at 4.49 ppm (\(J = 7.12\) Hz), The three protons on C3-4′-CH\(_3\) appeared as triplet at 1.43 ppm (\(J = 7.12\) Hz). The three protons on C6-OCH\(_3\) appeared as singlet at 3.98 ppm and the C2-CHO proton appeared at 10.37 ppm. The \(^13\)C NMR spectrum (Fig. S3) revealed the presence of 14 carbons and the values are 14.0(C3-4′-CH\(_3\)), 55.8(C6-OCH\(_3\)), 62.5(C3-3′-CH\(_2\)), 105.3(C5), 125.2(C3), 125.6(C7), 126.6(C9), 132(C8), 136.5(C4), 143(C10), 149(C2), 160.3(C6), 166.9(C3-\(\equiv\)O), 191.5(C2-CHO).

4.3. Powder X-ray diffraction analysis

Powder XRD pattern (Fig. S4) for the grown crystal 2F6M3CQ has been carried out using bruker D8 advance diffractometer. The sample was scanned for 2\(\theta\) values from the range 5–50\(°\) at the scan rate of 2\(°\) per minute. The Bragg’s peak of the above crystal was very sharp and hence the synthesized crystal possesses good degree of crystallinity.

4.4. UV-visible spectroscopy

The experimental UV–Vis spectrum of 2F6M3CQ was recorded in methanol medium and it is depicted in Fig. 1. The \(\lambda_{\text{max}}\) value of 2F6M3CQ is affected by substitutions in the aromatic ring and also by the hetero atoms. The solvent effects were also found to be pronounced, since the polarity of methanol alters the wavelength of absorption. The substituent in the benzene ring push or pull electrons hence the transition energy of electrons can be altered. The absorption bands at 207, 237 and 319 nm in ultraviolet region corresponds to \(\pi-\pi^*\) and n-\(\pi^*\) transitions. The first absorption band observed at 207 nm is attributed to the solvent; the lower cut-off methanol lies in this range. The strong absorption band at 237 nm, corresponds to the symmetry forbidden \(\pi-\pi^*\) transition in benzene, while it is symmetry allowed in pyridine because of lower symmetry introduced by N-atom. Furthermore N-atom of pyridine ring is conjugated to carbonyl group; hence it leads to bathochromic shift. The B-band of n-\(\pi^*\) transitions of quinoline is observed at 315 nm, while in the case of 2F6M3CQ crystal it was observed at 319 nm, the slight change in wavelength shift is attributed to the conjugation of N-atom with the carbonyl bond. The n-\(\pi^*\) transitions of carbonyl group takes place in the range of 310–330 nm, these excitation may also be coupled with n-\(\pi^*\) transitions of the pyridine moiety [37].

Lower cutoff wavelength of 2F6M3CQ is 236 nm, the high percentage of transmission in the entire visible region confirms it optical activity. The optical band gap of the material was calculated by using absorption data. The (E\(_g\))\(_{\text{cryst}}\) was calculated by extrapolating the straight
line to the x-axis as shown in Fig. 2. The crystal shows two band gaps at 4.955 eV and 5.648 eV hence it can be a potent applicant for optoelectronic applications.

4.5. Photoluminescence analysis

Photoluminescence spectra (PL) was analyzed to understand the electronic structure of the crystal. The emission spectrum of 2F6M3CQ was recorded from 300 to 600 nm in methanol medium and the corresponding plot of wavelength versus intensity is shown in Fig. 3. The crystal compound shows two emission bands violet emission corresponds to 362 nm and blue emission at 492 nm. The strong emission band and longer wavelengths confirms the presence of intermolecular interactions, this indicates that crystal is stable and can be used to design new drug materials.

4.6. Single crystal X-ray diffraction analysis

The crystal structure of a synthesized compound 2F6M3CQ was established by single crystal X-ray diffraction analysis. Good optical quality crystal of dimensions 0.4 × 0.3 × 0.3 mm was chosen for analysis. The compound crystallized into monoclinic symmetry with centrosymmetric P21/c space group with four molecules in unit cell. The unit cell parameters are a = 7.4158 (7) Å, b = 20.341 (2) Å, c = 8.4653 (7) Å, α = γ = 90° and β = 97.314 (4)° with volume 1266.6 (2) Å³. The crystal structure was solved by SHELXS-97 [38] by direct method and refined by full matrix least squares in F̅2 [39]. The refinement of the structure led to R value R1 = 0.481 and wR2 = 0.1279. The crystallographic data and refinement details are shown in Table S1. The ortep diagram of the molecule with 50% probability level of thermal displacement ellipsoids with the atom numbering scheme is shown in Fig. 4.

Packing diagram along a, b, and c axis is depicted showing hydrogen bonding interactions of all kind Fig. 5. The crystal structure was stabilized by H–H interactions and O–H interactions predominantly. Intra molecular hydrogen bond is also present in the crystal between ester group oxygen and formyl hydrogen atom.

The crystal structure exhibits intermolecular C–H⋯N (C2–H2⋯N1, 2.687 Å, 169.7°) and C–H⋯O (C7–H7⋯O3, 2.601 Å, 144.9°) charge less hydrogen bonding interactions which strongly influence the stability of a crystal structure. The data regarding hydrogen bonding geometry of the title compound is shown in Table S3. The carbonyl oxygen atom (O3) forms bifurcated hydrogen bond with H5 and H7 of adjacent molecule in crystal lattice with bond length 2.627 Å and 2.601 Å respectively. Nitrogen atom (N1) interacts with H2B of ethoxy group with bond distance 2.687 Å. Fig. 6 shows extended intermolecular hydrogen bonding network present in the crystal which enhance the binding ability of a chemical molecule with amino acid moieties of a protein molecule.

5. Computational study

5.1. Computational methodology

All the calculations were performed using Gaussian 16 suite of programs [40]. The optimization of compound 2F6M3CQ is performed using density functional theory (DFT) method at B3LYP/6-311G* level of theory. The B3LYP/6-311G* level of theory is usually considered as gateway methodology for doing calculations in combined experimental and computational studies [41–44]. A subsequent frequency calculation is performed to check that optimized geometry with all positive values and a global minimum. The UV–Visible spectrum of compound 2F6M3CQ is calculated using time dependent-density functional theory (TD-DFT) at same level of theory. The molecular docking studies are performed through a grid base technology as implemented in AutoDockVina [45]. The MGL tools [46] and discovery studio visualize [46] is used for input file preparations and visualization of intermolecular interactions, respectively. Several replicate docking attempts are made to get the most suitable docked model with good binding energy and intermolecular interactions. Further details about protein and ligand preparations can be seen in our previous studies [47–49]. For prediction of ADME properties, swissadme online server (www.swissadme.ch) was used [50].

5.2. Molecular geometry of compound 2F6M3CQ

The geometry optimization of compound 2F6M3CQ was performed to get its lowest energy molecular structure. A comparative perspective of calculated and experimental geometries is given in Fig. 6. Both the geometries are shown side by side and clearly it can be seen that there is very good agreement among the calculated and experimental geometrical parameters. For instance, the methoxy group shows exactly the same values for experimental and calculated geometries. The calculated bond lengths of N atom and carbon atoms were also found to be 1.352 Å and 1.321 Å for C24=N28 and N28=C25 bonds respectively, which were very close to experimental values of 1.352 Å and 1.319 Å for C24=N28 and N28=C25 bonds, respectively. The calculated bond lengths of carbonyl groups are found to be 1.207 Å and 1.206 Å for C8=O32 and C8=O31 bonds, which are near to their respective experimental values of 1.192 Å and 1.197 Å for C8=O32 and C8=O31 bonds, respectively. The molecular structure of compound 2F6M3CQ is planar and only ethyl acetate group is slightly out of plane with a calculated (experimental)
Fig. 6. A graphical and numerical values comparison for molecular geometry of 2F6M3CQ.

Fig. 7. The UV–Visible spectrum of 2F6M3CQ molecule at TD-M06/6-311G* level of theory while insight shows its experimental UV–Visible spectrum.

Fig. 8. (a) The 3-dimensional illustration of FMOs including HOMO, HOMO-3 and LUMO orbitals. (b) The molecular electrostatic potential diagram of compound 2F6M3CQ where red and blue colours indicate negative and positive maximum. The iso-values are ±0.002 a. u.
torsion angle of 48.86° (62.99°) which perhaps due to compression stress in solid-state experimental forms.

5.3. Quantum chemically calculated UV–visible spectrum of 2F6M3CQ

The TD-M06 method is used to calculate the vertical excitation in the form of UV–Visible spectrum for compound 2F6M3CQ. The calculated UV–Visible spectrum of compound 2F6M3CQ is shown in Fig. 7 where experimentally calculated spectrum is also shown as insight figure. Experimentally reported spectrum of compound 2F6M3CQ shows three absorption peaks at 207, 237 and 319 nm having lower, highest and the lowest intensities, respectively. The quantum chemically calculated spectrum also shows the similar three peaks at 194, 241 and 316 nm having lower, highest and the lowest intensities, respectively. Overall there is very good agreement between calculated and experimentally UV–Visible spectra of compound 2F6M3CQ where all the three absorption peaks are reproduced well in semi-quantitative way. The difference of 13, 4, 3 nm among the calculated and experimental peaks which is explainable due the lack of proper exchange and correlation effects in adopted functional. A careful analysis of excitation energies show that the calculated absorption wavelength at 316 nm is from HOMO to LUMO orbitals with its configuration interaction of 63% as compared with others while on the other hands, 194 and 241 nm absorptions mainly involve HOMO-3 to LUMO and HOMO-1 to LUMO+3, respectively. The distribution of these orbitals will be visualized and discussed in proceeding sections.

5.4. Frontier molecular orbitals and MEP of 2F6M3CQ

The frontier molecular orbitals are very crucial to guess the reactivity and kinetic stability of any compound. In our TD-DFT calculations, we found that important transitions originate from HOMO to LUMO and HOMO-3 to LUMO in the lowest energy and highest intensity of transitions. These orbitals are drawn in 3-dimensional space as given in Fig. 8 (a). Careful analysis of orbitals shows that there is redistribution of electronic density upon absorption transitions. The transition from HOMO-3 to LUMO also involves the redistribution of electron density from ethyl acetate group to the remaining moiety of compound 2F6M3CQ. There is no clear donor-acceptor configuration perhaps due to which the absorption remains in UV region of absorption spectrum.

Besides FMOs, we have also drawn the molecular electrostatic potential diagram to see the overall charge distribution in the optimized ground state of compound 2F6M3CQ. The MEP is very informative to see different reactive sites of a molecular compound [51]. The MEP of compound 2F6M3CQ is shown in Fig. 8(b). The analysis of Fig. 8(b) illustrates the negative potential around –CHO and –COOC6H5 groups while a positive potential surface is seen for hydrogen atoms. The uneven distribution of MEP shows the good ability for intermolecular interactions as studied in preceding sections.

5.5. Molecular docking study

In view of current pandemic of COVID-19, we have considered our compound worthy to investigate for its potential against SARS-CoV-2 which causes COVID-19. For this purpose the crucial protein of main protease (Mpro, PDBID:6LU7) is selected to study the molecular docking interactions. The Mpro is very crucial protein which helps in the replication of SARS-CoV-2 virus inside the host. There are three main domains on the surface of Mpro protein including domains I, II and III. The domains I and II possess catalytic cavity while domain III dimeric and

Table 1

The calculated binding free energy (kcal/mol), predicted inhibition constant (K_i, μmol) and intermolecular interactions between ligand (2F6M3CQ) and Mpro protein.

| Binding Free Energy kcal/mol | Predicted inhibition constant (K_i, μmol) | Intermolecular Interactions (Ligand-Protein) |
|-----------------------------|------------------------------------------|---------------------------------------------|
| H-Bonds | Electrostatic | Hydrophobic |
| Lig-ARG131 (3.008 Å) | Lig-ASN289 (5.54 Å) | Lig-LEU287 (4.490 Å) |
| Lig-LEU286 (5.220 Å) | Lig-LEU287 (5.329 Å) |
| Lig-LEU287 (3.211 Å) | Lig-THR199 (1.927 Å) |
| Lig-THR199 (2.908 Å) | Lig-LEU287 (3.008 Å) |

Fig. 9. The 3-D representation of Mpro with its docked ligand where (a) illustrates the overview of whole protein cartoon structure (b) shows its focused view with labelled interacting residues (c) shows reacting cavity in total density surface and its H-bond donor and acceptor surfaces with pink and green colours, respectively.
intra domain interface which are also very crucial. We have made several replicate docking attempts and finally selected ligand-protein complex where ligand is docked in intra domain as shown in Fig. 9. An overview of docked ligand with whole $M^{\text{pro}}$ protein is shown in Fig. 9 (a) while same docked model is represented over total density surface of $M^{\text{pro}}$. The total density surface shows a good visual docking model with nicely fit ligand inside the intra domain cavity. The focused view of ligand interacting inside the protein residues is shown in Fig. 9(b) where hydrogen bond distances are measured and labelled. There are around eight interaction as seen from Fig. 9(b) including four hydrogen bonds, three hydrophobic and one electrostatic interaction between ligand and residues of $M^{\text{pro}}$ protein. All the distances of these intermolecular interactions are given in Table 1 along with the binding free energy calculations. The calculated binding free energy between ligand and $M^{\text{pro}}$ protein is found to be $-5.5 \text{ kcal/mol}$ and apredicted inhibition constant of $89.90 \mu\text{mol}$. A negative value of binding free energy indicates that the ligand is more stable in bound state than alone. For semi-quantitative comparison, we have also docked similar chloroquine molecule in the same binding domain as compound 2F6M3CQ. The overall docked models of both molecules are shown in Fig. 10. The binding energy of chloroquine molecule is found to be $-4.5 \text{ kcal/mol}$, which is about $1 \text{ kcal/mol}$ less than our docked molecule (see Fig. S7 of supporting information). This gives a semi-quantitative insight that our synthesized molecule might have better inhibition properties than chloroquine molecule. Regarding the intermolecular interactions in ligand-$M^{\text{pro}}$ complex, two $H$-bonds are observed between ligand and two hydrophilic amino acid residues (arginine and threonine) while one $H$-bond is seen between ligand and hydrophobic aliphatic leucine residue. The only electrostatic interaction is illustrated between ligand and amodic asparagine residue. Finally, two leucine residues form three hydrophobic interactions with ligand. Overall, the good fit of ligand within the cavity of intra domain III is considered as result of above mentioned important intermolecular interactions.

5.6. Drug likeness and ADME properties of 2F6M3CQ

Apart from good binding free energy and intermolecular interactions, the drug likeness and ADME properties are very crucial to guess a candidate molecule for its medicinal importance. There are several parameters which are usually considered as important to calculate the drug likeness consisting of ADME properties, Lipinski Rule of five (RO5), bioavailability radar and boiled egg techniques etc. It is important to mention that these techniques are not equivalent to their experimental counterparts but these are accurate enough to predict properties of interest in a semi-quantitative way because these techniques are based on rigorous data analysis. There is no violation found for RO5 in our above entitled compound 2F6M3CQ. The bioavailability radar also shows all parameters well inside permissible limits except molecular saturation which is slightly out of limit (see Fig. 10(a)). Fig. 10(b) indicates the BOILED-Egg plot for compound 2F6M3CQ. An analysis of plot shows that compound 2F6M3CQ is predicted as brain penetrated (in the yolk) and red dot shows it is not subject to active efflux, which is encouraging for its drug likeness properties. These predictive ADME analyses indicates several drug like properties of compound 2F6M3CQ and its potential to use as drug for SARS-CoV-2 inhibitor.

6. Conclusion

The title compound 2-formyl-6-methoxy-3-carbethoxy quinoline has been synthesized and characterized through UV–Vis–NIR, $^1\text{H}$ and $^{13}\text{C}$ NMR spectroscopic techniques. The crystals of the compound were grown by slow solvent evaporation technique and crystal structure was established by single crystal x-ray diffraction method. The title compound was crystallized into monoclinic crystal system with centrosymmetric $P2_1/C$ space group with four molecules in unit cell. The crystal exhibits inter molecular interactions which plays main role in interaction with biological molecules. UV–Vis–NIR analysis show absorption in UV region and there is no appreciable absorption in visible region. The PL analysis shows presence of intermolecular interactions, this indicates the stability of the crystal and can be used to design new drug materials.

The quantum chemically optimized molecular geometry and UV–Vis spectrum was found in good agreement with their respective experimental results. Molecular docking results suggested the druggability of 2F6M3CQ with $M^{\text{pro}}$protein of SARS-CoV-2. Several crucial intermolecular interactions between $M^{\text{pro}}$protein and 2F6M3CQ molecule caused a good binding energy between ligand and protein with even better binding energy than chloroquine molecule as studied under same computational protocols. The drug likeness and ADME properties of 2F6M3CQ were also analyzed which predicted that 2F6M3CQ might be a potential inhibitor candidate for SARS-CoV-2.

Credit authors statement

A. Franklin Ebenazer: Conceptualization, Methodology, Writing - Original Draft.
M. Saravanabhavan: Project administration, Funding acquisition, Resources, Data Curation, Writing - Original Draft.
K.S.Ramesh: Conceptualization, Formal analysis, Writing - Review & Editing.
Shabbir Muhammad: computational quantum chemical study, software and writing results and discussions.
Abdullah G. Al-Sehemi: Project administration and acquiring of fundings.
N. Sampathkumar: Supervision Project administration, Writing - Review & Editing.

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.

Data availability
The data has been used is confidential.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpcs.2022.110886.
CCDC: 2104606 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336033) or E-mail: deposit@ccdc.cam.ac.uk.

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