

Synthesis, characterization, nonlinear optical properties theoretical and molecular docking studies of Cu(II) complex with 1,10-phenanthroline

Shraddha Choudhary^a, Shail Kumari Singh^a and Sampat Prasad Rawat^{a*}

Department of Chemistry, Govt. Vivekanand P. G. College Maihar -485771, Satna, M. P. India.

[a]* Corresponding Author: sprawat@hotmail.com; drsambatprasad.rawat@gmail.com

Manuscript received online 03 March 2022, accepted on 18 July 2022

Abstract : In this work, we describes the synthesis, structural characterization, nonlinear optical properties, quantum computational investigation and molecular docking studies of copper (II) coordination complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its counterpart cationic Cu(II) complex $C_{36}H_{24}CuN_6$ (**1b**) for developments to find a potential antiviral drug and /or inhibitor for the main protease (M^{pro}) of COVID-19 spike protein [where, HL=4-bromo-2-((Z)-(naphthalene-4-ylimino) methyl)phenol, phen = 1,10-phenanthroline]. The inhibition of COVID-19 main protease (M^{pro}) with copper (II) complex will eventually lead to the destruction of COVID-19 virus. Single crystal X-ray analysis of copper (II) complex (**1a**) has revealed the presence of a distorted octahedral geometry around mononuclear copper (II) center. Molecular docking revealed that complex $[Cu(II)(phen)_3]^{2+}$ (**1b**) possessed high binding affinity and inhibition constant with the receptor protein of COVID-19 compared with known antiviral drugs. The third order NLO polarizability values range between as high as $205.05 \times 10^{-36} \text{esu}$ and as low as $147.92 \times 10^{-36} \text{esu}$ for complexes copper (II) complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its counterpart cationic complex $C_{36}H_{24}CuN_6$ (**1b**). Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). As potential applications, we have also evaluated the predicted ligand and copper (II) complex through ADME descriptors. The ADME analysis showed that ligand and complex are non-carcinogenic and less toxic than standard antiviral drugs.

(Keywords : Antiviral drug; SARS-CoV-2; Copper (II) complex, main protease (M^{pro}); Potential inhibitor; COVID-19)

Introduction

The world is currently fighting a COVID-19 pandemic. The end of 2019 marked the emergence of a deadly and highly contagious new coronavirus, the COVID-19-nCoV which now officially termed as the SARS-CoV-2 or the Novel Coronavirus¹. There has been a rapid out-break of a novel pneumonia-like illness mainly originating by an unknown pathogen emerged in the city of Wuhan, Capital of Hubei Province, Central China^{2,4}, which was later coined as COVID-19. The recent outbreak of the coronavirus disease COVID-19 is putting the world towards a great threat. It has recently been declared as a pandemic by the World Health Organization⁵. It is a challenging process though vital to discover fruitful drugs against SARS-CoV-2. Having no alternatives, favipiravir, remdesivir, chloroquine, and hydroxychloroquine that are previously designed antiviral drugs for the treatment of COVID-19. Finding a therapeutic agent to treat COVID-19 is matter of great current interest. One target that has received much attention is the SARS (severe acute respiratory syndrome) CoV-2 main protease (M^{pro})^{6,7}. SARS-Cov-2 virus genes encode four structural proteins, nucleocapsid (N), membrane (M), spike (S) and envelop (E) which are common features to all COVID-19 coronaviruses⁸.

There are vast amount of research on organic compounds and metal complexes has been recently conducted to discover drugs for

efficacious treatment of corona virus disease 2019 (COVID-19) reported so far⁹⁻³⁰. Metal chelates as potential compounds to block SARS-CoV-2, which is very vital for attracting the coronavirus to its host cell. Thus inhibition of COVID-19 main protease spike protein with metal complex will eventually lead to the destruction of COVID-19 virus^{31, 32}. Organic molecules have been intensively studied for the treatment of COVID-19, but less attention has been made using metal complexes as anti-COVID main protease (M^{pro}) drug to fight against the novel coronavirus. Copper can be a powerful weapon in the fight against COVID-19 and future pandemics, but we have to use it as copper compounds. Throughout history, copper alloys or their compounds were recognized for their antimicrobial activity³³. As the world is witnessing severe damages of COVID-19, it is immensely important to explore every possible opportunity for its possible therapeutic drug or cure. Many different drugs^{34, 35} are under testing in clinical trials to assess their efficacy against COVID-19. Hence it is a great challenge for finding a therapeutic agent to treat COVID-19 virus. Considering the metal complexes as COVID-19 main protease drug to fight against the novel corona virus and also inspiring by recent developments to find a potential inhibitor for the COVID-19 virus, herein, copper (II) coordination complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its counterpart cationic complex $C_{36}H_{24}CuN_6$ (**1b**) was synthesized and its interaction with main protease (M^{pro}) of COVID-19 spike protein is studied by molecular docking methods to find a possible therapeutic drug candidate for COVID-19. The third order NLO polarizability values rang between as high as 205.05×10^{-36} esu and as low as 147.92×10^{-36} esu for complexes copper (II) complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its counterpart cationic complex $C_{36}H_{24}CuN_6$ (**1b**). Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). In addition, Swiss-ADME analysis of studied complex was also incorporated in this study. Thus, we believe the present study will provoke not only the interest

of scientific community in the synthesized complex but also incite the drug designing community.

2. Experimental

2.1. Methods and Materials

2.1 Chemicals

All chemicals and solvents for this work was used as received.

2.2. X-ray structure determination

Single crystal suitable for X-ray analysis was mounted on glass fibers and used for data collection. The structure were solved by direct methods using the program SHELXS-97³⁶ and refined by full-matrix least-square techniques against F^2 using SHELXL-97³⁷. The ORTEP diagram with the atom numbering scheme was shown in Figure 2. Anisotropic refinement was used for all non-hydrogen atoms. Hydrogen atoms were placed geometrically and held in the riding model.

2.3 Molecular Docking Protocols

The AutoDockVina (ADV) program is used for docking studies in the present investigation. ADV offers more accuracy in analyzing protein-ligand interactions as compared to Autodock 4.2 where the aforementioned provides more accuracy for a ligand by analyzing more than twenty rotatable bonds^{38,39}. In addition to this, the water molecules and previously crystalized co-ligand were removed from the receptor molecule through the Auto Dock GUI program⁴⁰. The docking protocol was validated by docking previously crystalized co-ligands with the M^{pro} protein. The visualization of results was performed using a free version of Discovery Studio visualizer⁴¹.

2.4 Swiss-ADME descriptors

To be effective as drug candidates, the preliminary test in the potential application for theoretical biological activities of ligand and its complex (**1a**) and (**1b**) have been evaluated by Swiss-ADME; a free web tool to evaluate

pharmacokinetics, drug likeness and medicinal chemistry friendliness of small molecules⁴³. Easy efficient input and interpretation are ensured thanks to a user-friendly interface through the login-free website <http://www.swissadme.ch>.

2.5 General procedure for synthesis

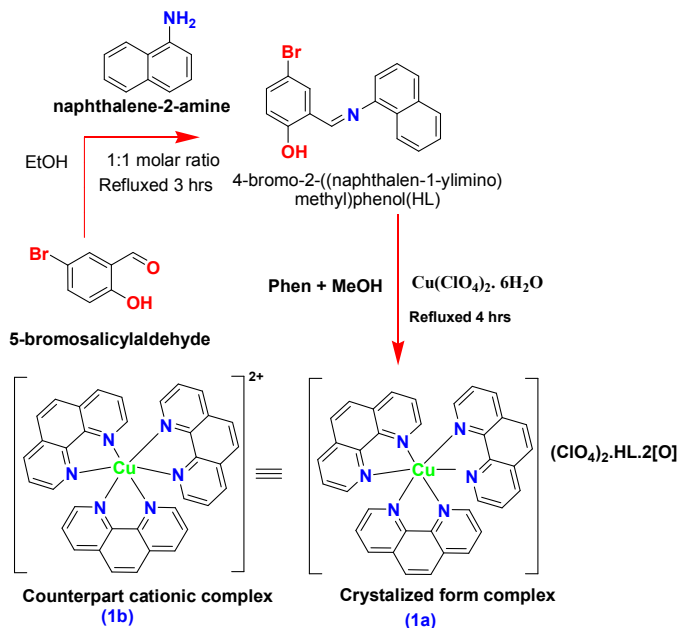
Schiff base ligand (HL) and its copper (II) complex were synthesized as reported methods⁴⁴. Anal. Calc. for $C_{17}H_{12}BrNO$ (%): C, 62.60; H, 3.71; N, 4.29. Found (%): C, 62.62; H, 3.73; N, 4.30. FAB-mass (m/z): Obs. (Calcd.): 326.19 (326). FT-IR (KBr/cm^{-1}): 1604 ($>C=N$); 3109 and 1224 ($\delta Ar-OH$). UV-Vis (MeOH) 501 nm: 360, 470. ^1H -NMR (400 MHz, $DMSO-d_6$): δ 12.98 (1H, s, Ar-OH), 8.99 (1H, s, imine C-H), 8.18-8.15 (1H, m, J = 8 Hz, 4 Hz, Ar-H), 8.00-7.98 (2H, d, J = 8 Hz, Ar-H), 7.91-7.89 (1H, d, J = 8 Hz, Ar-H), 7.62-7.59 (1H, m, J = 8 Hz, 4 Hz, Ar-H), 7.41-7.40 (1H, d, J = 4 Hz, Ar-H), 7.04-7.02 (1H, d, J = 8 Hz, Ar-H), 3.37 (s, H_2O), 2.57-2.50 (s, DMSO). Anal. Calcd. for (1a) (%): C, 56.45; H, 3.38; N, 9.60. Found (%): C, 56.53; H, 3.42; N,

9.67. FAB-mass (m/z): Obs. (Calcd.): 1172.31 (1172). FTIR (KBr/cm^{-1}): 441-423 (Cu-N), 781-768 (phen). UV-Vis (MeOH) 501 nm: 409, 354, 310.

3. Results and Discussion

3.1 Synthesis and characterization

Scheme 1 represent protocol used for the synthesis of HL and its copper (II) complex (1a) and (1b) is reported in Scheme 1. Characterization of synthesized copper complex was carried out by several spectroscopic techniques. The computational exploration for novel functional properties of the title complexes were also incorporated in the study. The refined single crystal structures are further subjected to computational studies at molecular and bulk levels using DFT and ab initio methods, respectively. The optimized geometries of the complex as well as their electronic structures have been analysed through DFT calculations. The compounds were soluble in most of the organic solvents but insoluble in water, stable towards O_2 and moisture.



Scheme 1. Representative structure and synthetic route of Schiff base and copper (II) complex.

3.2 Crystal structures description

The geometries of copper complex have also been confirmed by single crystal X-ray study. Single-crystal X-ray diffraction reveals that the complex (**1a**) is mononuclear. The copper(II) center is in a distorted octahedral geometry with a N_6 donor environment. The ORTEP representation with atom numbering scheme is shown in Figure 1. Crystallographic data and molecular structure refinement important interatomic parameters are given in Table 1. The relevant bond angles and lengths are presented in Table 2. The complex (**1a**) crystallized in the triclinic system of the space group $P-1$ with two molecules in the unit cell. In complex (**1b**), the copper (II) ion shows a distorted octahedral geometry where three 1, 10-phenanthroline molecules occupy the equatorial and axial plane. As shown in Figure 1, the copper (II) center is in a distorted octahedral geometry with a N_6 donor atoms of 1, 10-phenanthroline. Here, 4-bromo-2-((Z)-(naphthalene-4-ylimino) methyl) phenol (HL) is a bidentate ligand and it is not bonded with Cu (II) atom, but it resides in crystal structure of complex (**1a**). One free molecule of water molecule is also found in the solution of crystal structure of complex (**1a**). Bond distances of all six nitrogen and copper are different. The Cu-N bond lengths around the copper(II) ions are [N(1)-Cu(1)=2.239(4), N(6)-Cu(1)=2.065(3), N(5)-Cu(1)=2.083(4), N(3)-Cu(1)=2.206(4), N(4)-Cu(1)=2.068(3) and N(2)-Cu(1)=2.118(4) Å. The *trans* bond angles are [N(1)-Cu(1)-N(4)=93.21(14)°, N(2)-Cu(1)-N(5)=92.35(14)° and N(3)-Cu(1)-N(6)=95.38(11)°]. These values are similar to the recently reported analogues copper (II) complexes^{44, 45}. In this complex, the slight distortion in the basal plane may be attributed for the strain imposed by the tris-chelating ligands (three molecule of 1, 10-phenanthroline) to the metal center during the coordination.

3.3 Quantum chemical study

The quantum computation can provide the insights into structure-property relationship of several materials, which are not possible with conventional characterization instruments due to

their intrinsic limitations. Along the similar lines, the computational studies about the coordination compounds has quickly swelled up where it is used with reasonable accuracy to correlate and explain the structural features and functional properties of coordination complexes^{46,47}. All quantum chemical calculations were carried out using the Gaussian 09 program package⁴⁸. We have only considered the quantum chemical calculation study including frontier molecular orbitals (FMOs), electrostatic potential diagrams and global reactivity parameters (stability as well as reactivity) of copper (II) cationic complex (**1b**).

The frontier molecular orbitals (FMOs) play a crucial role in understanding the nature of intramolecular charge transfer processes in chemical compounds. The FMOs are also crucial for predicting the reactivity of chemical compounds. The FMOs including LUMO and HOMO along with their orbital energies (eV), energy gaps (eV) for cationic complex (**1b**) are drawn in Figure 2. An overview of Figure 2 shows that in complex (**1b**), its HOMO and LUMO orbitals are nearly degenerate as shown by a small energy gap and a similar distribution pattern between these two orbitals (LUMO = -8.67 eV, HOMO = -11.96 eV, HOMO-2 = -12.21 eV, HOMO-3 = -12.34.67 eV). The HOMO and LUMO orbitals mainly involved in lowest energy transitions which have very low or negligible oscillator strengths, so we have drawn the orbitals which involved in transitions possessing larger oscillator strengths (Table 3). As shown in Table 3, the oscillator strength (f_o) should be at least 0.02 to be considered as significant. The energies of HOMO and LUMO were used to depict global reactivity parameters (stability as well as reactivity) of copper (II) cationic complex (**1b**). Overall, the electron donating and accepting abilities were described by ionization potential and electron affinity. In the studied complex (**1b**), the ionization potential was found to be much higher than electron affinity (A) values. The stability as well as reactivity of a chemical system was correlated to chemical potential and global

hardness values⁵⁰. The stability had a direct relation with global hardness, whereas it had an inverse relationship to its reactivity⁵¹.

Furthermore, we have made the electrostatic potential diagrams for complex (**1b**) in Figure 3. The electrostatic potential diagrams indicate the regions of positive and negative electron densities in blue and red color coding, respectively. It is suggested that in a MEP plot, the maximum positive region that is the preferred site for nucleophilic attack is indicated with blue colour. Similarly, a maximum negative region which is the preferred site for electrophilic attack is indicated as a red surface. As shown in Figure 3, due to cationic, its all surface is positive (Blue) in the molecular electrostatic potential maps (MEPs) of cationic complex (**1b**).

3.4 Molecular docking, binding affinity and interactions

There are several copper complexes which showed good inhibition properties against different biological species⁵²⁻⁵⁴. As our copper complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its cationic $C_{36}H_{24}CuN_6$ (**1b**) is a novel synthesis so it is also pertinent to see its effectiveness as a potential inhibitor against SARS-CoV-2. For this purpose, we have docked the copper complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its cationic $C_{36}H_{24}CuN_6$ (**1b**) with main protease (M^{pro}) of spike protein (PDB ID: 6LU7 and 6MOK) of SARS-CoV-2, which is very vital for attaching the virus to its host cell⁵⁵. In Table 4, we have collected the molecular docking results for copper complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its cationic $C_{36}H_{24}CuN_6$ (**1b**) and M^{pro} . These include the most important parameters including the binding affinity, inhibition constant and different amino acid residues of M^{pro} that interacts with the copper complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its cationic $C_{36}H_{24}CuN_6$ (**1b**). The binding affinity and inhibition constant were found to be -8.400 kcal/mol and 0.661 μ M, respectively, for the best-docked confirmation of (**1b**) complex with M^{pro}

protein. This binding affinity is reasonably well as compared to recently known antiviral drugs. For instance, the binding affinity of (**1b**) complex is found to be better than recently docked results of chloroquine (-6.293 kcal/mol), hydroxychloroquine (-5.573 kcal/mol) and remdesivir (-6.352 kcal/mol) with M^{pro} protein⁵⁵.

Apart from the binding affinity and inhibition constant values, it is also very important to visualize the intermolecular interactions between complex $C_{53}H_{35}BrCl_2CuN_7O_{11}$ (**1a**) and its cationic $C_{36}H_{24}CuN_6$ (**1b**) complex and M^{pro} protein as shown in Figure 4-12. There is observed one δ -hydrogen bond with a distance of 2.432 Å between NH_2 of GLN110 residue and δ -electrons of phenanthroline moiety of complex (**1b**). Besides the pi-hydrogen bond, there is also seen one δ -anionic electrostatic interaction between δ -orbitals of ligand and (COO⁻) group of anionic ASP 153 residue. The third kind of two interactions is seen as hydrophobic, which are between the δ -electrons of ligand and δ -electrons of PHE 294 residues with distances of 5.086 Å and 4.667 Å. The fourth kind of interaction is also hydrophobic which is between δ -electrons of ligand and alkyl group of VAL 104 residue. An intuitive view of the docking cavity is presented in Figure 4-12 by calculating the total density surfaces of M^{pro} protein along with the docked (**1b**) complex based on H-bonding and hydrophobic interactions as shown in Figure 2(a) and 3(b), respectively. The total density surface with H-bond donor is those residues which possess polar hydrogen atoms and represented with green mesh color while H-bond acceptor is those protein residues which possess electronegative atoms and represented with pink mesh colors. The results obtained from molecular docking indicates that there are H-bond and hydrophobic interactions between of M^{pro} protein and (**1b**) complex, which is often considered as crucial factors for potential inhabitation activity. Similar observations was found for complex (**1a**);

3.5 *In-silico* ADME study

The *in-silico* Swiss-ADME predicted that the ligand HL and its copper(II) complex (**1a**) and its cationic complex (**1b**) shows positive response to both blood brain barrier and human intestinal absorption as shown in Table 6. The ligand was found to be non-carcinogenic and does not inhibit the P-glycoprotein. Therefore, it has protective capacity to interrupt the absorption, permeability, and retention of the drugs⁵⁶. Ligand HL along with hydroxychloroquine shows type III acute oral toxicity. Ligand HL indicates good inhibitor for human ether-a-go-go-related gene (hERG) that can lead to short QT syndrome⁵⁷. Drug development involves assessment of absorption, distribution, metabolism and excretion (ADME) increasingly earlier in the drug discovery process, at a stage when considered compounds are numerous, but access to the physical samples is limited. In that context, computer models have been fostered as a valid alternative to experimental procedures for prediction of ADME at the early steps of drug discovery⁵⁸. A large variety of *in silico* methods share the objective of predicting ADME parameters from molecular structure and their pharmacokinetic and physicochemical parameters^{59,60}. Swiss-ADME is providing a collection of free Web-based tools covering many aspects of computer-aided drug design (CADD). The physicochemical properties like molecular weight (MW), molecular refractivity (MR), count of specific atom types and polar surface areas (PSA) are compiled in Bioavailability Radar section which shows important properties for oral bioavailability. The bioavailability radar of HL, complex (**1a**) and its cationic complex (**1b**) molecules based on well-absorbed and poorly absorbed their lipophilicity and polarity as described by the n-octanol/water partition coefficient (log-P) and the polar surface area (PSA). The physicochemical space for oral bioavailability of the molecules represents the optimal range for each properties (lipophilicity: XLOGP3 = 4.81, size: MW = 326.19 g/mol, polarity:

TPSA = 32.59 Å², solubility: logS = -6.94, saturation: Fraction Csp³ = 0.00, flexibility: number of rotatable bonds = 2 for **HL**; lipophilicity: XLOGP3 = 15.58, size: MW = 1160.23 g/mol, polarity: TPSA = 204.67 Å², solubility: logS = -10.22, saturation: Fraction Csp³ = 0.00, and flexibility: number of rotatable bonds = 6 for (**1a**); lipophilicity: XLOGP3 = 6.77, size: MW = 604.16 g/mol, polarity: TPSA = 29.58 Å², solubility: logS = -10.22, saturation: Fraction Csp³ = 0.00, and flexibility: number of rotatable bonds = 0 for (**1b**). These compounds are predicted not orally bioavailable, because too flexible and too polar structures.

The preliminary test in the theoretical biological activities were also evaluated using the Brain or Intestinal Estimated permeation method (BOILED-Egg) that works by computing the lipophilicity and polarity of small molecules. The BOILED-Egg allows for intuitive evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) in function of the position of the molecules in the WLOGP-versus-TPSA referential (Pharmacokinetics: BBB permeant = Yes, P-gp substrate = Yes, CYP1A2/ CYP2C19/ CYP2C9 = Yes, CYP2D6/ CYP3A4 inhibitor = No, Log Kp (skin permeation) = -4.87 cm/s, drug-likeness: bioavailability score = 0.55, medicinal chemistry: PAINS = 0, drug-likeness = No, synthetic accessibility = 2.68 for **HL**; BBB permeant = No, P-gp substrate = No, CYP1A2/ CYP2C19/ CYP2C9/ CYP2D6/ CYP3A4 inhibitor = No, Log Kp (skin permeation) = -2.34 cm/s, drug-likeness: bioavailability score = 0.17, medicinal chemistry: PAINS = 0, drug-likeness = No, Synthetic accessibility = 6.40 for (**1a**); BBB permeant = No, P-gp substrate = No, CYP1A2/ CYP2C19/ CYP2C9/ CYP2D8/ CYP3A4 inhibitor = No, Log Kp (skin permeation) = -5.18 cm/s, drug-likeness: bioavailability score = 0.55, medicinal chemistry: PAINS = 0, drug-likeness = No, Synthetic accessibility = 4.01 for (**1b**). The complex (**1a**) and its cationic complex (**1b**) were predicted as not absorbed and not BBB penetrant (outside the Egg) as compared with standard drug

(streptomycin with a TPSA of 331.43 Å² and a WLOGP of -7.74).

Third-order NLO polarizabilities

All the calculations in present study were performed using Gaussian 16 suit of programs for copper (II) complex C₅₃H₃₅BrCl₂CuN₇O₁₁ (**1a**) and its counterpart cationic complex C₃₆H₂₄CuN₆ (**1b**). The ground state geometries were optimized with M06 functional and 6-311G* basis sets (Table 5 and 6). For the calculation of nonlinear optical (NLO) polarizability, a finite field (FF) method is used within T-convention and its details are given in different literature^{42,44}. The following expressions were used to calculate the average (γ) third-order NLO polarizability:

$$\langle \gamma \rangle = \frac{1}{15} \sum_{ij=x,y,z} (\gamma_{ijij} + \gamma_{ijji} + \gamma_{ijji}). \quad (1)$$

Under Kleinmann symmetry, the static NLO polarizability components are limited to only six components as given below:

$$\langle \gamma \rangle = \frac{1}{5} (\gamma_{xxxx} + \gamma_{yyyy} + \gamma_{zzzz} + 2(\gamma_{xxyy} + \gamma_{xxzz} + \gamma_{yyzz})). \quad (2)$$

The third order NLO polarizability values rang between as high as 205.05 × 10⁻³⁶esu and as low as 147.92 × 10⁻³⁶esu for complexes copper (II) complex C₅₃H₃₅BrCl₂CuN₇O₁₁ (**1a**) and its counterpart cationic complex C₃₆H₂₄CuN₆ (**1b**). Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). To make a quantitative comparison that the above synthesized systems possess adequate NLO responses to be utilized as promising candidate in various research dimensions, comparison with some reference molecules and some similar compounds has also been made, which may ensure its implication in NLO device fabrication technology based on expression of perturbation theory is given as:

$$\gamma_{iiii} = 24 \sum_{n \neq g} \left[\frac{(\mu_{ng}^i \Delta \mu_{ng}^i)^4}{(E_{ng})^8} - \frac{(\mu_{ng}^i)^4}{(E_{ng})^8} + \sum_{m \neq n, g} \frac{(\mu_{ng}^i)^2 (\mu_{mn}^i)^2}{(E_{ng})^2 E_{mg}} \right] \quad (3)$$

Where $\Delta \mu_{ng}^i$ represents difference between excited and ground state, μ_{ng}^i represents the change in dipole in *i*-th direction, while E_{ng} shows energy value involved in crucial transition. A careful look of the above-mentioned approximation reveals that *g* value mainly depends on the *g* terms. It is obvious from Table 5 and 6 that complexes copper (II) complex C₅₃H₃₅BrCl₂CuN₇O₁₁ (**1a**) and its counterpart cationic complex C₃₆H₂₄CuN₆ (**1b**) higher *g* values, lower transition energies while higher change in dipole moments values.

Conclusions

We have successfully reported the synthesis of copper (II) complex C₅₃H₃₅BrCl₂CuN₇O₁₁ (**1a**) and its counterpart cationic complex C₃₆H₂₄CuN₆ (**1b**). This study gives a clear ideal that the structural and functional properties of copper (II) complex (**1a**) and its cationic complex (**1b**), may be highly effective for inhibiting M^{pro} which is main protease for SARS-CoV-2 causing the deadly disease COVID-19. Swiss-ADME analysis showed that copper (II) complex C₅₃H₃₅BrCl₂CuN₇O₁₁ (**1a**) and its counterpart cationic complex C₃₆H₂₄CuN₆ (**1b**) were predicted as not absorbed, not BBB penetrant, and also not orally bioavailable due to flexible and too polar structures. The third order NLO polarizability values rang between as high as 205.05 × 10⁻³⁶esu and as low as 147.92 × 10⁻³⁶esu for complexes copper (II) complex C₅₃H₃₅BrCl₂CuN₇O₁₁ (**1a**) and its counterpart cationic complex C₃₆H₂₄CuN₆ (**1b**). Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). To make a quantitative comparison that the above synthesized systems possess adequate NLO responses to be utilized as promising candidate in various research dimensions, comparison with some reference molecules and some similar compounds has also been made, which may ensure its implication in NLO device fabrication.

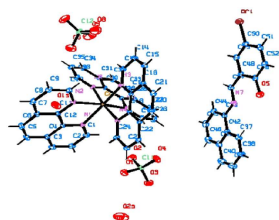


Figure 1. ORTEP structure of copper (II) complex (**1a**).

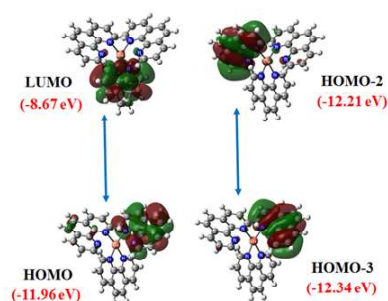


Figure 2. The frontier molecular orbitals including HOMO and LUMO along with their orbital energies (eV), energy gaps (eV) for cationic complex (**1b**).

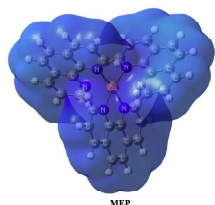


Figure 3. The molecular electrostatic potential maps (MEPs) of cationic complex (**1b**). Due to cationic, its all surface is positive (Blue) in MEP.

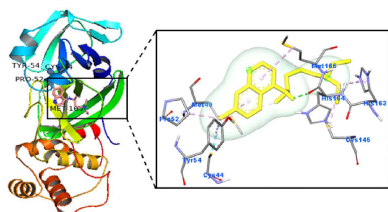


Figure 4. The docked Chloroquine inside the M^{Pro}protein (PDB ID: 6LU7) with its focused view for interacting residues around the docked ligand.

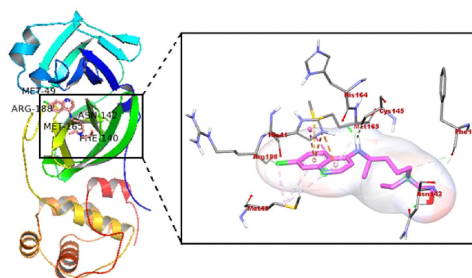


Figure 5. The docked Hydroxychloroquine inside the M^{Pro}protein (PDB ID: 6LU7) with its focused view for interacting residues around the docked ligand.

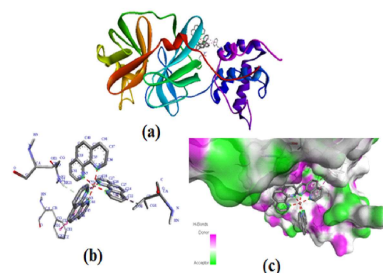


Figure 6. Docked conformations and nonbonding interactions of copper (II) complex (**1b**) and hydroxychloroquine at inhibition bounding site of main protease (M^{Pro}) of spike protein (PDB ID: 6LU7) of COVID-19.

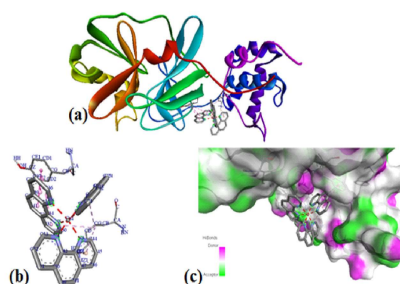


Figure 7. Molecular docking of copper (II) complex (**1b**) with main protease (M^{Pro}) of spike protein (PDB ID: 6LU7) of COVID-19 depicting the possible hydrogen bonding and hydrophobic Pi-Pi interactions in amino acid residues.

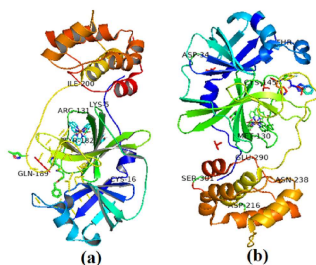


Figure 8. The docked copper (II) complex (**1a**) inside the COVID-19 main protease (PDB ID: (a) 6LU7 and (b) 6MOK) with its focused view for interacting residues around the docked complex.

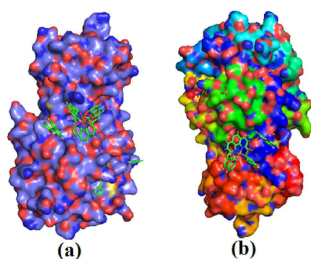


Figure.9. The total density surface representation of docked copper (II) complex (**1a**) inside the COVID-19 main protease (PDB ID: (a) 6LU7 and (b) 6MOK).

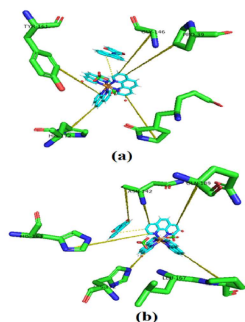


Figure 10. Surface presentation of docked copper (II) complex (**1a**) inside the COVID-19 main protease (PDB ID: (a) 6LU7 and (b) 6MOK).

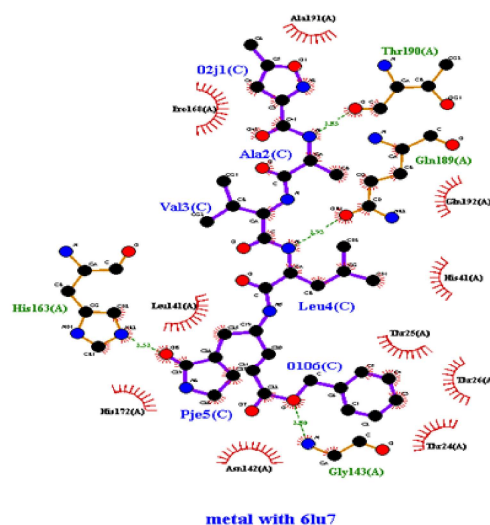


Figure 11. Molecular docking presentation of copper (II) complex (**1a**) with COVID-19 main protease (PDB ID: 6LU7).

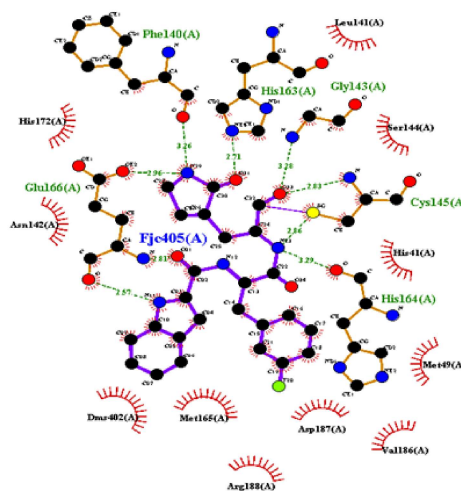


Figure 12. Molecular docking presentation of copper (II) complex (**1a**) with COVID-19 main protease (PDB ID: 6M).

Table 1.
Crystallographic data and refinement parameters for copper (II) complex (**1a**)

Crystallographic data	(1a)
Empirical formula	C ₅₃ H ₃₅ BrCl ₂ CuN ₇ O ₁₁
Formula weight (g mol ⁻¹)	1160.23
Temperature (K)	296 (2)
Wavelength, λ (Mo K α), (Å)	0.71073
Crystal system	Triclinic
Space group	P -1
<i>a</i> (Å)	12.3862 (7)
<i>b</i> (Å)	14.5961 (11)
<i>c</i> (Å)	14.8338 (13)
α (°)	74.255 (4)
β (°)	76.578 (4)
γ (°)	83.704 (3)
<i>V</i> (Å ³)	2507.6 (3)
<i>Z</i>	2
<i>D</i> _{calc} (g/cm ³)	1.537
μ (mm ⁻¹)	1.409
<i>F</i> (000)	1176
Crystal size (mm)	0.30 × 0.20 × 0.20
θ range for data collection (°)	1.45 to 28.65
Limiting indices	-16 < = <i>h</i> < = 16, -19 < = <i>k</i> < = 19, -15 < = <i>l</i> < = 20
Reflections collected/unique [<i>R</i> _{int} = 0.0297]	20960/12593
Completeness to theta (28.65%)	97.7
Absorption correction	Semi-empirical from equivalents
Max and Min transmission	0.7659 and 0.6773
Refinement method	Full-matrix least-square on <i>F</i> ²
Data/restraints/parameters	12593/0/677
Goodness-of-fit (GOF) on <i>F</i> ²	0.944
Final <i>R</i> indices [<i>I</i> > 2 σ (<i>I</i>)] ^a	<i>R</i> ₁ = 0.0701; <i>wR</i> ₂ = 0.1959
<i>R</i> indices (all data) ^b	<i>R</i> ₁ = 0.1269; <i>wR</i> ₂ = 0.2427
Extinction coefficient	0.0053(10)
Largest diff. peak & hole (Å ⁻³)	1.323 and -0.641

Table-2 Bond distances (Å) and bond angles (°) in complex (1a).

Bond lengths (Å)			
N(1)-Cu(1)	2.239(4)	N(6)-Cu(1)	2.065(3)
N(5)-Cu(1)	2.083(4)	N(3)-Cu(1)	2.206(4)
N(4)-Cu(1)	2.068(3)	N(2)-Cu(1)	2.118(4)
Bond angles (°)			
N(6)-Cu(1)-N(4)	171.72(14)	N(5)-Cu(1)-N(3)	97.36(14)
N(6)-Cu(1)-N(5)	80.13(14)	N(2)-Cu(1)-N(3)	94.72(14)
N(4)-Cu(1)-N(5)	95.53(14)	N(6)-Cu(1)-N(1)	93.21(14)
N(6)-Cu(1)-N(2)	92.44(13)	N(4)-Cu(1)-N(1)	94.02(14)
N(4)-Cu(1)-N(2)	93.17(13)	N(5)-Cu(1)-N(1)	92.35(14)
N(5)-Cu(1)-N(2)	166.34(14)	N(2)-Cu(1)-N(1)	76.53(14)
N(6)-Cu(1)-N(3)	95.38(14)	N(3)-Cu(1)-N(1)	168.01(14)
N(4)-Cu(1)-N(3)	78.10(13)		

Table - 3Global reactivity descriptors for copper (II) complex (**1b**)^a.

Complex(1b)	I	A	X	η	μ	ω	σ
	7.793	0.604	4.233	3.621	-4.219	2.432	0.1372

^aIonization potential (I), electro negativity (X), softness (σ), global hardness (η), and electron affinity (A), chemical potential (μ), global electrophilicity (ω).

Table 4.

The molecular docking results for copper(II) complex (**1b**) and M^{pro} including the binding affinity, inhibition constant and different amino acid residues of M^{pro} that interact with the ligands.

Binding Affinity (kcal/mol)	Inhibition Constant, Ki (μ M)	Interacting Protein Residues		
		H-Bond	Electrostatic	Hydrophobic
-8.400	0.661	GLN110:HE21 (2.432Å)	ASP 153 (4.993Å)	PHE 294 (5.086Å), PHE 294 (4.667Å), VAL 104 (5.144Å)

Table 5.

The calculated values ($\times 10^{-36}$ esu) along with its individual components as for complex (**1a**) and (**1b**) at M06/6-311G* levels of theory

γ	1(a)	1(b)
γ_{xxxx}	120.17	270.82
γ_{yyyy}	321.54	190.07
γ_{zzzz}	128.68	124.628
γ_{xxyy}	58.133	76.73
γ_{xxzz}	90.959	78.47
γ_{yyzz}	89.05	85.60
$\langle \gamma \rangle$	431.16	329.05

Table - 6

Calculated values of third-order polarizability and electronic excitations for for complex **(1a)** and **(1b)** at TD-M06/6-311G* level of theory.

complex	Electronic Excitation	ΔE (eV)	f_0	μ_{ng}	Transition	%C.I.
1(a)	S ₀ →S ₉	4.710	0.340	0.865	H-L→M+1	47
1(b)	S ₀ →S ₅	3.962	0.356	1.891	H-L→M	63

References

1. L. Mittal, A. Kumari, M. Srivastava, M. Singh, S. Asthana, *J. Biomol. Struct. Dyn.* 1-26 (2020)
2. K. Al-Khafaji, D. Al-Duhaidahawil, T. T. Tok, *J. Biomol. Struct. Dyn.* 1-11 (2020)
3. T. M. Abd El-Aziz, J. D. Stock, *Infect. Genet. Evol.* **83**,104327 (2020)
4. F. Wu, S. Zhao, B. Yu, Y.-M. Chen *et al.*, *Nature*, **579**,565 (2020)
5. T. Acter, N. Uddin, J. Das, A. Akhter, T. R. Choudhury, S. Kim, *Sci. Total Environ.* 138996 (2020).
6. J. J. Kozak, H. B. Gray, R. A. Garza-Lopez, *J. Inorg. Biochem.* **211**, 111179 (2020).
7. L. Zhang, D. Lin, X. Sun, U. Curth, C. Drosten, L. Sauerhering, S. Becker, K. Rox, R. Hilgenfeld, *Science*, **368**, 409 (2020).
8. S. Boopathia, A. B. Pomab, P. Kolandaivel, *J. Biomol. Struct. Dyn.* in press (2020).
9. N. van Doremalen, T. Bushmaker, D. H. Morris, *et al. N. Engl. J. Med.* **382**(16), 1564 (2020).
10. J. Gao, Z. Tian, X. Yang, *Biosci. Trends*, **14**, 72–73 (2020)
11. M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, *Cell Res.* **30**, 269 (2020)
12. M. C. Sportelli, D. Longano, E. Bonerba, G. Tantillo, L. Torsi, L. Sabbatini, N. Cioffi, N. Ditaranto, *Molecules*, **25**, 49 (2020).
13. G. Li, E. D. Clercq, *Nat. Rev. Drug Discov.* **19**, 149; (f) F. Touret, X. de Lamballerie, *Antivir. Res.* **177**, 104762 (2020)
14. J. T. Wu, K. Leung, M. Bushman, N. Kishore, R. Niehus, P. M. de Salazar, B. J. Cowling, M. Lipsitch, G. M. Leung, *Nat. Med.* **26**, 506 (2020)
15. T.P. Sheahan, A. C. Sims, S. R. Leist, A. Schäfer, J. Won, A. J. Brown, S. A. Montgomery, A. Hogg, D. Babusis, M. O. Clarke, J. E. Spahn, L. Bauer, S. Sellers, D. Porter, J. Y. Feng, T. Cihlar, R. Jordan, M. R. Denison, R. S. Baric, *Nat. Commun.* **11**, 1-14 (2020).
16. P. Das, R. Majumder, M. Mandal, P. Basak, *J. Biomol. Struct. Dyn.*, Doi: **10.1080/07391102.2020.1796799**. (2020)
17. R. Yadav, M. Imran, P. Dhamija, D. K. Chaurasia, S. Handu *J. Biomol. Struct. Dyn.*, Doi: 10.1080/07391102.2020.1796812 (2020).
18. N. Razzaghi-Asl, A. Ebadi, S. Shahabipour, D. Gholamin *J. Biomol. Struct. Dyn.*, Doi:10.1080/07391102.2020.1797536 (2020).
19. S. A. Kulkarni, S. K. Nagaranjan, V. Ramesh, V. Palaniyandi, S. P. Selvam, T. Madhavan, *J. Mol. Struct.*, **1221**,128823 (2020).
20. M. Venkateshan, M. Muthu, R. R. Kumar, *J. Mol. Struct.*, **1220**, 128741 (2020).

21. A. Chhetri, S. Chhetri, P. Rai, B. Sinha, D. Brahman, *J. Mol. Struct.*, **1224**, 129178 (2021).
22. N. Baildya, A. A. Khan, N. N. Ghosh, T. Dutta, A. P. Chattopadhyay, *J. Mol. Struct.*, **1227**, 129390 (2021).
23. W. B. Cardoso, S. A. Mendanha, *J. Mol. Struct.*, **1225**, 129143 (2021).
24. K. Ghosh, S. A. Amin, S. Gayen, T. Jha, *J. Mol. Struct.*, **1224**, 129026 (2021).
25. A. Powelczyk, L. Zaprutk, *Future Med. Chem.*, **12**(19), 1743 (2020).
26. M. N. Uddin, M. S. Amin, M. S. Rahman, S. Khandaker, W. Shumi, M. A. Rahman, S. M. Rahman, *Appl. Organomet. Chem.* **35**(1). 6067 (2021)
27. M. A. Mansour, A. M. Aboulmagd, H. M. Abdel-Rahman, *RSC Adv.*, **10**, 34033 (2020)
28. M. B. Alshammari, M. Ramadan, A. A. Aly, E. M. El-Sheref, M. A. Bakht, M. A. A. Ibrahim, A. M. Shawky, *J. Mol. Struct.*, **129649** (2020)
29. C. A. R.-Terbouche, H. Abdeldjebar, H. Lakhdari, K. Bachari, T. Roisnel, D. Hauchard, *J. Mol. Struct.*, **1222**, 128918 (2020).
30. A. S. M. Al-Janabi, A. O. Eljupir, T. A. Yousef, *J. Mol. Struct.*, **1228**, 129454 (2021).
31. T. A. Altalhi, K. Alswat, W. F. Alsanie, M. M. Ibrahim, A. A. Hamdy, S. E. -Sheshtwy, *J. Mol. Struct.*, **1228**, 129459 (2021).
32. N. Baildya, N. N. Ghosh, A. P. Chattopadhyay, *J. Mol. Struct.* **1219**, 128595 (2020).
33. H. T. Michels, C. A. Michels, *Curr. Trends Microbiol.*, **10**, 23 (2016)
34. F. J. Meyer-Almes, *Comput. Biol. Chem.*, **88**, 107351 (2020)
35. M. Pal, D. Musib, M. Roy, *New J. Chem.* **45**, 1924 (2021)
36. G.M. Sheldrick, *Acta Crystallogr. Sect. A* **46** 467. (1990)
37. G.M. Sheldrick, *Acta Crystallogr. Sect. A* **64** 112 (2008).
38. O. Trott, A. J. Olson, *J. Comput. Chem.*, **31**(2), 455 (2010)
39. A. Andreou, S. Trantza, D. Filippou, N. Sipsas, S. Tsiodras, *In Vivo, National Library of Medicine*, **34**(3), 1567 (2020)
40. G. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, *J. Comput. Chem.*, **30**(16), 2785 (2009)
41. D. S. Biovia, Discovery Studio Visualizer , v17.2.0, Dassault Systems San Diego, 2017. Google Scholar : There is no corresponding record for this reference.
42. B. Mohan, M. Choudhary, S. Muhammad, N. Das, K. Singh, A. Jana, S. Bharti, H. Algarni, A. G. Al-Sehemi, S. Kumar. *J. Coord. Chem.* **73**(8), 1256 (2020).
43. C.A. Lipinski, F. Lombardo, B. W. Dominy, P.J. Feeney, *Adv. Drug. Deliv. Rev.*, **46**, 3-26 (2001).
44. B. Mohan, S. Muhammad, A. G. Al-Sehemi, S. Bharti, S. Kumar, M. Choudhary, *Chemistry Select*, **6**, 738 (2021)
45. N. P. Juraj, M. Krklec, T. Novosel, B. Periae, R. Vianello, S. Raiae-Maliae, S. I. Kirin, *Dalton Trans.*, **49**, 9002 (2020)
46. K.G Vladimirova, A. YaFreidzon, O.V. Kotova, A.A. Vaschenko, L.S. Lepnev, A. A. Bagaturyants, A.G. Vitukhnovskiy, N.F. Stepanov, M.V. Alfimov, *Inorg. Chem.* **48** 11123 (2009)
47. J. Adhikary, P. Chakraborty, S. Das, T. Chattopadhyay, A. Bauza, S.K. Chattopadhyay, B. Ghosh, F.A. Mautner, A. Frontera, D. Das, *Inorg. Chem.* **52**, 13442 (2013)
48. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, Gaussian 09 citation; Gaussian Inc.: Wallingford, (2013).
49. M. M. Lawal, T. Govender, G. E. Maguire, H. G. Kruger, B. Honarparvar, *Int. J. Quantum Chem.*, **118**, 25497 (2017)
50. Y. Sert, S. Sreenivasa, H. Dogan, N. R. Mohan, P.A. Suchetan, F. Ucun, *Spectrochim. Acta, A.*, **130**, 96 (2014)
51. S. Murugavel, V. V. Velan, D. Kannan, M. Bakthadoss, *J. Mol. Struct.* **1108**, 150 (2016).
52. D. K. Johnson, T. B. Murphy, N. J. Rose, W. H. Goodwin, L. Pickart, *Inorg. Chim. Acta*, **67**, 159 (1982)
53. C. Banti, N. Kourkoumelis, A. Hatzidimitriou, I. Antoniadou, A. Dimou, M. Rallis, A. Hoffmann, M. Schmidtke, K. McGuire, D. Busath, A. Kolocouris, S. K. Hadjikakou, *Polyhedron*, **185**, 114590 (2020)
54. A. Andreou, S. Trantza, D. Filippou, N. Sipsas, S. Tsiodras, *In Vivo, Nat. Lib. Med.*, **34**, 1567 (2020).
55. S. Boopathi, A. B. Poma, P. Kolandaivel, *J. Biomol. Struct. Dyn.* **1** (2020)
56. A. Gleich, B. Kaiser, W. Honscha, H. Fuhrmann, A. Schoeniger, *Cytotechnology*, **71**, 231 (2019).

57. M. C. Sanguinetti, M. Tristani-Firouzi, *Nature*, 2006, 440, 463. J.L. Dahlin, J. Inglese, M.A. Walters. *Nat. Rev. Drug Discov.*, **14**, 279 (2015).
58. S. Tian, S.J. Wang, Y. Li, D. Li, L. Xu, T. Hou. *Adv. Drug Deliv. Rev.*, **86**, 2 (2015)
59. A. Daina, V. Zoete. *Chem. Med. Chem.*, **11**, 1117 (2016).
60. A. Daina, O. Michielin, V. Zoete, *Sci. Rep.*, **7**, 42717, (2017)