

Synthesis and study of copper (II) and Ni(II) complex with reference to theoretical biological applications, optical and nonlinear optical properties

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Abstract : This work report the synthesis, theoretical studies, antivirus properties and DFT calculations of copper (II) mixed ligand complex and its potential analogue with tridentate Schiff base and mono-/ bidentate co-ligands. A new Schiff base ligand (H_2L) and its a Cu(II) complex $[Cu(L)(bipy)]$ (**1**) and a Ni(II) complex $[Ni(L)(Me-ImH)]$ (**2**), (where $H_2L=(E)-2-((2-hydroxypyridine-3-yl)methyleneamino)benzoic$ acid, $bipy=2,2'$ -bipyridine, $Me-ImH=2$ -Methyl-imidazole as co-ligands) have been synthesized and designed. The synthesized ligand was coordinated to metal ions through the tridentate-ONO donor atoms. The newly synthesized complexes were characterized by various spectroscopic and physiochemical methods. DFT based quantum mechanical calculations have been performed on the Schiff base and its metal complexes to study the structure-property relationship. The third order NLO polarizability values rang between as high as $205.05 \times 10^{-36} esu$ and as low as $147.92 \times 10^{-36} esu$ for a Cu(II) complex $[Cu(L)(bipy)]$ (**1**) and a Ni(II) complex $[Ni(L)(Me-ImH)]$ (**2**) respectively. Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). The ' γ ' values for the studied systems lie in the order of a Cu(II) complex $[Cu(L)(bipy)]$ (**1**) and a Ni(II) complex $[Ni(L)(Me-ImH)]$ (**2**), successively calculated. Furthermore, the molecular docking studies of the metal complexes, a Cu(II) complex $[Cu(L)(bipy)]$ (**1**) and a Ni(II) complex $[Ni(L)(Me-ImH)]$ (**2**) with SARS-CoV-2 virus (PDB ID: 7DWY) are also investigated. The molecular docking calculations of a Cu(II) complex $[Cu(L)(bipy)]$ (**1**) and a Ni(II) complex $[Ni(L)(Me-ImH)]$ (**2**) with SARS-CoV-2 virus revealed that the binding affinities at inhibition binding site of receptor protein are -6.8 kcal/mol and -7.9 kcal/mol, respectively with inhibition constant 2.924 and 5.631 μM ,

respectively and the docking results are compared with Chloroquine (CQ) and Hydroxychloroquine (HCQ) as anti-SARS-CoV-2 drugs.

(Keywords : Tridentate Schiff base ligand, Cu(II) complex, Ni(II) complex, SARS-CoV-2 virus, DFT calculations.)

Introduction

Severe acute respiratory syndrome coronavirus-2 is the cause of COVID-19 pandemic¹. Drug repurposing against a pandemic may result in sudden crisis of an essential drug, while many repurposed drugs are under testing in clinical trials to assess their efficacy against COVID-19². Many investigators are searching for a therapeutic agent to treat SARS-CoV-2 infections. One target that has received much attention is the SARS-CoV-2 main protease (M^{pro})³, a homodimer whose structure has been determined. The structural biology and bioinformatics in the genetic code hidden within the ribonucleic acid (RNA) chain of the virus itself is one of huge obstacle that researchers have had to overcome when looking for a cure or vaccine. One of the first antiviral vaccines tested, the Ribavirin, a nucleoside analogue that acts as an RNA polymerase inhibitor, was used on patients with MERS and SARS-CoV-2 protease inhibitors⁴. Metal complexes are reported to inhibit potential anti-SARS-CoV-2 properties against COVID-19 virus by the mechanism of interfering with the primary viral pathogenetic processes, inhibition

of the viral entry into the host cells as well as inhibiting the RNA replication process or virus budding processes. Recently, several researchers have brought interest in copper well prior to the COVID-19 viral epidemic as an alternative source to make the immune system competent to fight against the SARS-CoV-2⁵.

Copper and nickel complexes of heterocyclic Schiff ligands are much interest to researcher in past several years. These having tridentate-ONO binding sites have been extensively synthesised and characterised. Moreover, copper and nickel have the ability to form different co-ordination environment and geometries giving large scope in co-ordination chemistry⁶. The variable donating properties of co-ordinating sites of Schiff base ligands produces complexes with structural diversities under different reaction conditions⁷. Recently, a series of copper and nickel complexes of Schiff base ligands having heterocyclic moiety has been synthesised and found that the nature of heteroatomic ring attached to them can considerably influence the biological activities of these complexes⁸⁻¹¹. These ligands and their complexes have been extensively studied exploring their biological properties, including antibacterial, antimalarial, antiviral, antioxidant, cytotoxic and antineoplastic¹²⁻¹⁵. Besides this, recently the world is in quest for effective drug to treat SARS-CoV-2. As virus effect is still on rise, there is an urgent need to develop effective drug to control the mortality rate which may rise in near future. A number of literatures are published exploring the anti-SARS-CoV-2 properties of Schiff base metal complexes¹⁶. Schiff bases metal complexes are known for their various antiviral properties have recently been identified for therapeutic strategies to combat SARS-CoV-2.¹⁷ In context to recent demands molecular docking approach has been applied for screening of metal complexes as potential inhibitors against with SARS-CoV-2. There is a remarkable in silico studies related to SARS-CoV-2 indicating the importance of metal complexes of Mn, Pd, V, Ni, Zn, Cu, Au, Pt etc. as potent inhibitor of against SARS-CoV-2 virus.^{18,19}

Herein, this work report the synthesis, theoretical studies, antivirus properties and DFT calculations of copper (II) mixed ligand complex and its potential analogue with tridentate Schiff base and mono-/bidentate co-ligands. A new Schiff base ligand (**H₂L**) and its a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**), (where H₂L= (E)-2-((2-hydroxypyridine-3-yl)methyleneamino)benzoic acid, bipy= 2,2'-bipyridine, Me-ImH= 2-Methyl-imidazole as co-ligands) have been synthesized and designed. The synthesized ligand was coordinated to metal ions through the tridentate-ONO donor atoms. The newly synthesized complexes were characterized by various spectroscopic and physiochemical methods. DFT based quantum mechanical calculations have been performed on the Schiff base and its metal complexes to study the structure-property relationship. 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 a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**) respectively. Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA).

The ' γ ' values for the studied systems lie in the order of a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**), successively calculated. Furthermore, the molecular docking studies of the metal complexes, a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**) with SARS-CoV-2 virus (PDB ID: 7DWY) are also investigated. The molecular docking calculations of a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**) with SARS-CoV-2 virus revealed that the binding affinities at inhibition binding site of receptor protein are -6.8 kcal/mol and -7.9 kcal/mol, respectively with inhibition constant 2.924 and 5.631 μ M, respectively and the docking results are compared with Chloroquine (CQ) and Hydroxychloroquine (HCQ) as anti-SARS-CoV-2 drugs.

2. Experimental

2.1. Methods and Materials

2.1 Chemicals

All chemicals and the solvents used in this analysis were of analytical grade and used as procured. 2-Hydroxypyridine-3-carbaldehyde, anthranilic acid, 2-Methylimidazole, copper(II) acetate monohydrate, nickel(II) acetatetetrahydrate salt were obtained from Sigma-Aldrich and used without further purification.

2.2 Characterization techniques

Various physical and spectral methods were investigated for the characterization of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2). Elemental analytical data and quantum mechanical calculations also applied for these purposes. The electronic spectra of the ligands and its complexes were taken on a Thermo scientific UV-Vis recording spectrophotometer Evolution-3000 in quartz cells. IR spectra were recorded in KBr medium on a Bruker-Alpha-Platinum-ATR spectrophotometer (400-4000 cm^{-1}). The C, H, and N determinations were made on an ElementarVario EL III Carlo Erba 1108 analyzer for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2).

2.3 Theoretical study

Theoretical calculations by density functional theory (DFT) were performed with regard to molecular structure optimization and HOMO-LUMO energies, etc. for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2). The geometry optimization of the ligands and complexes was performed at the $\text{ùB97X-D/6-311+G}^{**}$ level of theory in vacuum using the Gaussian16 software package²⁰ and cross-validated using the Spartan 16/18 parallel suite of programs²¹. The dispersion-corrected DFT functional ùB97X-D^{22} was chosen to accurately estimate the Vander walls interactions, which are expected to contribute greatly to the stability of

the complexes. Global reactivity descriptors (units in eV), such as ionization potential (IP), electron affinity (EA), electro negativity (χ), chemical potential (μ), global hardness (η), global softness (σ) and global electrophilicity (ω), were calculated using the formula as based on Koopmans theorem.

2.4 Molecular docking and analysis

The molecular docking studies were performed for the a Cu(II) complex [Cu(L)(ImH)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) to analyze their binding affinity for selected virus proteins. The crystal structures based on Structural basis for the different states of the spike protein of SARS-CoV-2 in complex with ACE2 of SARS-CoV-2 main protease was obtained from the Protein Data Bank²³ (PDB ID: 7DWY) and used as receptor protein. Initially, the protein coordinates were refined by deleting all the water and heteroatoms to make the targeted protein receptor-free. Further, the polar hydrogens and Kollman charges were added to the protein using the *Autodock tool* (ADT) 1.5.6 associated with *Autodock 4.2* software²⁴. The prepared protein and ligand coordinates are saved in a pdbqt file format using ADT software. The grid box of the desired volume is selected in such a way that the ligand can rotate freely inside the active site pocket protein. The configuration files are generated using the coordinates and dimension of the grid box. *Vina Lamarckian* genetic algorithm²⁵ generates the output files having predicted free energy for binding sites. The result comprises of different poses with corresponding energies were analyzed and high-quality figures are rendered by open-source Discovery Studio visualizer²⁶.

2.5 General procedure for synthesis

2.5.1 Synthesis of Schiff base ligand

To synthesize the targeted Schiff base ligand (**H₂L**), 2-hydroxypyridine-3-carbaldehyde (1.0 mmol) was taken in ethanol (10 mL) with

dropwise addition of ethanolic solution of anthranilic acid (1.0 mmol). The stirred mixture was refluxed for 2-3 h. Off-white colour shiny crude product was obtained. Anal. Calcd for $C_{13}H_{10}N_2O_3$ (**H₂L**): C, 64.46%; H, 4.16%; N, 11.56%. Found: C, 64.47%; H, 4.17%; N, 11.57%.; FAB-mass (m/z): Obs. (Calcd.) 242.07 (242 g/mol.); IR data (KBr/cm⁻¹): 1589 (>C=N), 3292(ν O-H). UV-Vis (DMSO) λ (nm): 360(π-π*) and 370(n-π*).

2.5.2. Synthesis of [Cu(L)(bipy)] (1)

To a solution of **H₂L** (1 mmol, 0.261g) in acetonitrile (10 mL), triethylamine (1.0 mmol, 0.680 mL) is added dropwise. The mixture was stirred for half an hour by adding 2,2'-bipyridine (1.0 mmol). This mixture was then added dropwise to the methanolic solution of copper(II) acetate monohydrate salt (0.5 mmol, 0.100g). The resultant solution was stirred for 4-5 hrs. After completion of reaction, the reaction mixture was filtered and was left for slow evaporation at room temperature. Brown colour precipitate was obtained which were filtered-off, dried in air and stored in a desiccator. Anal. Calcd for $C_{23}H_{16}CuN_4O_3$ (**1**): C, 60.06%; H, 3.51%; N, 12.18%. Found: C, 60.07%; H, 3.52%; N, 12.19%. FAB-mass (m/z): Obs. (Calcd.) 459.05 (459 g/mol.); IR data (KBr/cm⁻¹): 1620 (>C=N), 566(ν Cu-O), 540(ν Cu-N). UV-Vis (DMSO) λ (nm): 270 (π-π*) and 480(n-π*).

2.5.3. Synthesis of [Ni(L)(Me-ImH)] (2)

[Ni(L)(Me-ImH)] (**2**) was synthesized in a similar fashion as [Cu(L)(bipy)] (**1**) by adding nickel(II) acetate tetrahydrate salt (0.5 mmol, 0.124g) instead of copper(II) acetate monohydrate salt (0.5 mmol, 0.100g) and Me-ImH (1.0 mmol). The resultant solution was stirred for 4-5 hrs. After completion of reaction, the reaction mixture was filtered and was left for slow evaporation at room temperature. Green colour weak crystals were obtained which were filtered-off, dried in air and stored in desiccators. Anal. Calcd. for $C_{17}H_{14}N_4NiO_3$ (**2**): C, 53.59%; H, 3.70%; N, 14.70%. Found: C, 53.60%; H, 3.71%;

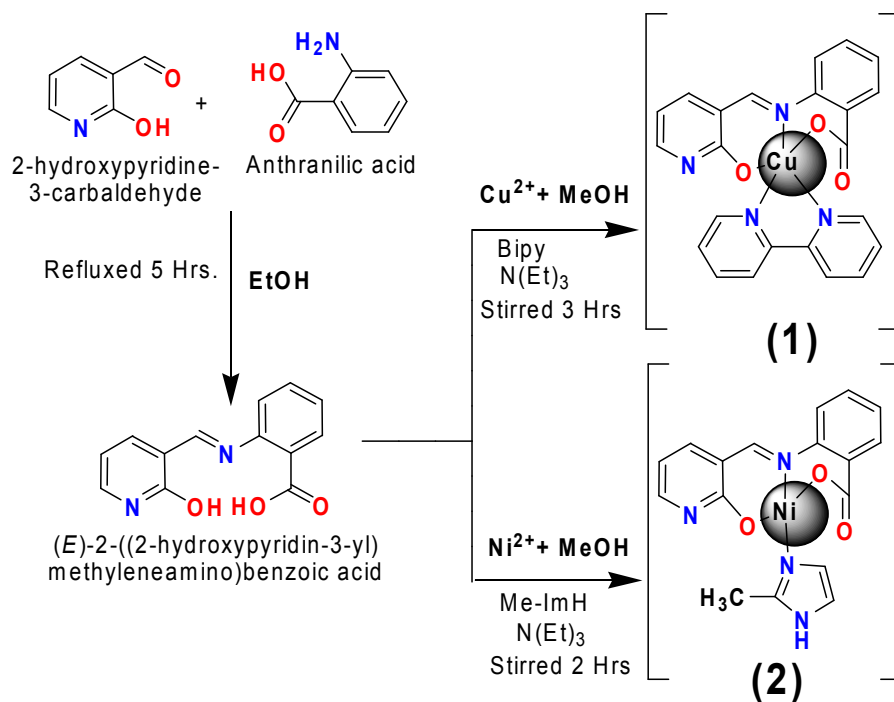
N, 14.71%. FAB-mass (m/z): Obs. (Calcd.) 380.04 (380 g/mol.); IR data (KBr/cm⁻¹): 1662 (>C=N), 632 (ν Ni-O), 573 (ν Ni-N). UV-Vis (DMSO) λ (nm): 280 (π-π*) and 520(n-π*).

3. Results and Discussion

3.1. Synthesis and characterization

Scheme 1 shows the synthetic routes for the Schiff base ligand (**H₂L**) and its a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**). This work report the synthesis, theoretical studies, antiviral properties and DFT calculations of copper (II) mixed ligand complex and its potential analogue with tridentate Schiff base and mono-/bidentate co-ligands.

A new Schiff base ligand (**H₂L**) and its a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**), (where **H₂L** = (E)-2-((2-hydroxypyridine-3-yl) methyleneamino) benzoic acid, bipy = 2,2'-bipyridine, Me-ImH = 2-Methyl-imidazole as co-ligands) have been synthesized and designed. The synthesized ligand was coordinated to metal ions through the tridentate-ONO donor atoms. The newly synthesized complexes were characterized by various spectroscopic and physicochemical methods. DFT based quantum mechanical calculations have been performed on the Schiff base and its metal complexes to study the structure-property relationship. Furthermore, the molecular docking studies of the metal complexes, a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**) with SARS-CoV-2 virus (PDB ID: 7DWY) are also investigated. The molecular docking calculations of a Cu(II) complex [Cu(L)(bipy)] (**1**) and a Ni(II) complex [Ni(L)(Me-ImH)] (**2**) with SARS-CoV-2 virus revealed that the binding affinities at inhibition binding site of receptor protein are -6.8 kcal/mol and -7.9 kcal/mol, respectively with inhibition constant 2.924 and 5.631 μM, respectively and the docking results are compared with Chloroquine (CQ) and Hydroxychloroquine (HCQ) as anti-SARS-CoV-2 drugs.



Scheme 1. Synthetic routes for the Schiff base ligand (H_2L) and its Cu(II) complex $[\text{Cu}(\text{L})(\text{bipy})]$ (**1**) and a Ni(II) complex $[\text{Ni}(\text{L})(\text{Me-ImH})]$ (**2**).

3.2 Quantum computational analysis

DFT has been proved to be best approach to investigate theoretically structure-property relationship for a compound as it shows excellent solution when both accuracy and computational time are taken in account¹¹. Figure 1 shows optimized and molecular structures of a Cu(II) complex $[\text{Cu}(\text{L})(\text{bipy})]$ (**1**) and a Ni(II) complex $[\text{Ni}(\text{L})(\text{Me-ImH})]$ (**2**) with atom numbering scheme derived from DFT method. FMO analysis provides the parameters for calculating the FMO energy gap which is used for describing the electronic structure of the compound^{27,28}. 3D plots of frontier molecular orbital (FMOs) for a Cu(II) complex $[\text{Cu}(\text{L})(\text{bipy})]$ (**1**) and a Ni(II) complex $[\text{Ni}(\text{L})(\text{Et-ImH})]$ (**2**) are given in Figure 3 and 4 respectively. During HOMO-LUMO analysis, the relevant occupied and unoccupied MOs (HOMO/LUMO, HOMO-1/LUMO+1 and HOMO-2/LUMO+2) are considered. The energy gaps are

calculated and shown in Table 1. It was noticed that for a Cu(II) complex $[\text{Cu}(\text{L})(\text{bipy})]$ (**1**) and a Ni(II) complex $[\text{Ni}(\text{L})(\text{Me-ImH})]$ (**2**). The calculated molecular electrostatic potentials (MEPs) maps and electron density surfaces for a Cu(II) complex $[\text{Cu}(\text{L})(\text{bipy})]$ (**1**) and a Ni(II) complex $[\text{Ni}(\text{L})(\text{Me-ImH})]$ (**2**) are given in Figure 4 and 5, which illustrates the three-dimensional charge distributions within the molecules²⁹. The MEPs is very useful descriptors to identify the electrophilic and nucleophilic reactive sites. Electrostatic potential map is drawn in the range -1.39 eV to -0.70 eV for a Cu(II) complex $[\text{Cu}(\text{L})(\text{bipy})]$ (**1**); while -1.72 eV to -1.06 eV for a Ni(II) complex $[\text{Ni}(\text{L})(\text{Me-ImH})]$ (**2**). The red color represents the more electronegative sites and the positive sites are represented by blue color. Global reactivity descriptors (units in eV), such as ionization potential (IP), electron affinity (EA), electro potential (ϕ), chemical potential (μ), global hardness (χ), global softness (σ) and global

electrophilicity (χ), were calculated for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) using the formulas based on Koopmans theorem[30]. The values of the global reactivity parameters for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) are listed in Table 2. Overall, the electron donating and accepting abilities were described by ionization potential and electron affinity³¹. The Global reactivity parameters (GRPs) explicated that all the complexes showed greater electron affinity (EA) than the ionization potential (IP) (Table 2); hence, complexes have greater electron-accepting ability. The stability as well as reactivity of a chemical system was correlated to chemical potential and global hardness values³¹. The stability had a direct relation with global hardness, whereas it had an inverse relationship to its reactivity³². Thus, from the result obtain we can conclude that a Cu(II) complex [Cu(L)(bipy)] (1) is most stable having highest global hardness compared to a Ni(II) complex [Ni(L)(Me-ImH)] (2).

3.3 Molecular docking and analysis

Molecular docking sheds light on designing drugs for the treatment of many diseases³³. This technique allows us to study the binding of ligands to proteins having greater significance to screen virtual libraries of drug-like molecules³⁴. For this consideration, we have purposefully docked all the synthesized compounds with the main protease (M^{pro}) of protein (PDB ID: 7DWY) of SARS-CoV-2. In Table3, we have listed the obtained molecular docking results for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2). Figure 6 shows The docked Cu(II) complex [Cu(L)(bipy)] (1) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues around the docked complex while Figure 7 indicated that the docked Ni(II) complex [Ni(L)(Me-ImH)] (2) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues around the docked complex. These display the most important parameters including

the binding affinity and different amino acid residues of M^{pro} that interact with the complexes. Furthermore, the molecular docking studies of the metal complexes, a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) with SARS-CoV-2 virus (PDB ID: 7DWY) are also investigated. The molecular docking calculations of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) with SARS-CoV-2 virus revealed that the binding affinities at inhibition binding site of receptor protein are -6.8 kcal/mol and -7.9 kcal/mol, respectively with inhibition constant 2.924 and 5.631 μ M, respectively and the docking results are compared with Chloroquine (CQ) and Hydroxychloroquine (HCQ) as anti-SARS-CoV-2 drugs.

Figure 8 show the representation of a docked Cu(II) complex [Cu(L)(bipy)] (1) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues along with H bond and intermolecular interactions; (a) H-bond donor and acceptor meshes represented by pink and light green colors, respectively; (b) Aromatic receptor surface represented by blue(Edge) and orange(face) colors; (c) Hydrophobic pocket represented with blue and brown colors; (d) ionizability receptor surface represented by blue (basic) and red (acidic) colors; (e) interpolated charge receptor surface represented by blue and red colors; (f) SAS receptor surface represented by blue and green colors, respectively. Figure 9 indicated that the representation of a docked Ni(II) complex [Ni(L)(Me-ImH)] (2) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues along with H bond and intermolecular interactions; (a) H-bond donor and acceptor meshes represented by pink and light green colors, respectively; (b) Aromatic receptor surface represented by blue(Edge) and orange(face) colors; (c) Hydrophobic pocket represented with blue and brown colors; (d) ionizability receptor surface represented by blue (basic) and red (acidic) colors; (e) interpolated charge receptor surface represented by blue and red colors; (f) SAS receptor surface represented

by blue and green colors, respectively. Figure 10 shows a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) is docked into the binding cavity of the receptor protein interaction of SARS-CoV-2 M^{pro} (PDB ID: 7DWY); The molecular re-docking study showed in surface view and 3D protein backbone with ligand (complexes) represented as a cartoon and corresponding 2D complex interaction plot. These binding affinities are reasonably well as compared to recently docked results of anti-SARS-CoV-2 drugs like chloroquine, hydroxychloroquine, and remdesivir with M^{pro} protein and the binding affinities of the studied new Schiff base ligand and their metal complexes were found to be better than other metal complexes reported using molecular docking techniques³⁵⁻³⁷.

3.4 Optical and non-linear optical properties

All the calculations in present study were performed using Gaussian 16 suit of programs for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2). The ground state geometries were optimized with M06 functional and 6-311G* basis sets. The M06 functional is relatively new functional and well tested for its ability to reliably predict many molecular properties by Truhlar group³⁸. All the geometries were fully optimized and subsequently the TD-M06 method is used to calculate their transition energies and orbital related information. 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 and in our previous studies³⁹. The following expressions were used to calculate the average $\langle\gamma\rangle$ third-order NLO polarizability:

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

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

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

3.5 third-order NLO polarizabilities

The Table 4 accommodates third-order NLO polarizability values (γ) for our studied systems along with its individual componential amplitudes along x, y and z-axes. The third order NLO polarizability values range between as high as 205.05×10^{-36} esu and as low as 147.92×10^{-36} esu for a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) respectively. Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). The ' γ ' values for the studied systems lie in the order of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2), successively, as given in Table 4.

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 etc. As illustrated, the considered systems display approximately 7-10 times more ' γ ' amplitudes (from the ratio 'h') as compared to reference para-nitro aniline (p-NA) molecule with the highest peak valued at 10 times larger for systems a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) respectively express higher ' γ ' values as compared to other heterocyclic derivatives, for instance, a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) respectively exhibits 65.63×10^{-36} and 68.99×10^{-36} esu in case of static γ value while 94.93×10^{-36} and 101.56×10^{-36} esu dynamic third order polarizability values for its isolated and embedded configurations, respectively at CAM-B3LYP/6-311+G(d) level of theory. Similarly, Schiff base carry 162.06×10^{-36} and 180.69×10^{-36} esu of γ amplitudes at TDHF method. As a fact, two most significant parameters have been taken into account transition energy and transition dipole moment (Table 4) to uncover the basis of second order non-linear hyper-polarizability values. According to perturbation

theory analysis in which type-I contributes positively to the overall γ term, amongst its three-level approximation expressions as delineated by others⁴⁰. The type-I expression of perturbation theory is given as:

$$\gamma_{iii} = 24 \sum_{n \neq g} \left[\frac{(\mu_{ng}^i \Delta \mu_{ng}^i)}{(E_{ng})^3} - \frac{(\mu_{ng}^i)^4}{(E_{ng})^5} + \sum_{m \neq n, g} \frac{(\mu_{ng}^i)^2 (\mu_{mn}^i)^2}{(E_{ng})^5 E_{mg}} \right] \quad (3)$$

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 and terms. It is obvious from Table 5 that a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) expresses higher g values, lower transition energies while higher change in dipole moments values. These results are quite promising with the above mentioned three-levels approximation, while for the rest of the moieties the alterations in dipole moment and transition energies are in such a way putting a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) at the lowest number in terms of increasing g value ordering.

Conclusions

In conclusion, we successfully synthesized and designed two new coordination complexes, a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2). The synthesized ligand was coordinated to metal ions

through the tridentate-ONO donor atoms. The newly synthesized complexes were characterized by various spectroscopic and physiochemical methods. DFT based quantum mechanical calculations have been performed on the Schiff base and its metal complexes to study the structure-property relationship. Furthermore, the molecular docking studies of the metal complexes, a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) with SARS-CoV-2 virus (PDB ID: 7DWY) are also investigated. The molecular docking calculations of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) with SARS-CoV-2 virus revealed that the binding affinities at inhibition binding site of receptor protein are -6.8 kcal/mol and -7.9 kcal/mol, respectively with inhibition constant 2.924 and 5.631 μ M, respectively and the docking results are compared with Chloroquine (CQ) and Hydroxychloroquine (HCQ) as anti-SARS-CoV-2 drugs. Furthermore, 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 a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) respectively. Calculation of third order polarizability property is important as it is referred as a characteristic sign for two-photon adsorption process (TPA). The ' γ ' values for the studied systems lie in the order of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2), successively calculated.

Table 1.

The HOMO and LUMO energies and the energy gap (ΔE)^a of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2).

Complexes	E _{LUMO}	E _{HOMO}	ΔE	E _{LUMO+1}	E _{HOMO-1}	ΔE	E _{LUMO+2}	E _{HOMO-2}	ΔE
(1)	-8.127	-1.114	-7.013	-5.187	-1.552	-3.635	-7.183	-2.661	-4.522
(2)	-5.624	-1.688	-3.936	-6.118	-2.114	-4.004	-4.528	-7.154	-2.626

^a Energy gap (" E ") = E_{LUMO} - E_{HOMO}, units in eV.

Table 2.

Global reactivity descriptors ^a of the of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2).

Molecular descriptors	Mathematical description	(1)	(2)
Ionization potential (IP)	$IP = -E_{HOMO}$	-0.27	-0.39
electron affinity (EA)	$EA = -E_{LUMO}$	-0.53	-0.61
electro negativity (χ)	$\chi = (IP + EA)/2$	-0.76	-0.83
chemical potential (μ)	$\eta = (IP - EA)/2$	0.17	0.32
global softness (σ)	$\mu = -(IP + EA)/2$	0.96	0.73
global hardness (η)	$\sigma = 1/2\eta$	4.85	3.48
Electrophilicity index (ω)	$\omega = \mu^2 / 2 \eta$	2.33	1.85

Table 3.

The molecular docking results a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) and M^{pro} including the binding affinity, inhibition constant and different amino acid residues of M^{pro} that interact with the ligand.

Complexes		Binding affinity (kcal/mol)	Inhibition constant, Ki (μM)	Interacting protein residues		
				H-bond	Electrostatic	Hydrophobic
(1)	7DWY	-6.8	2.924	HIS-49(3.71Å)	SER-967(4.82Å)	LYS-964(3.70Å)
(2)	7DWY	-7.9	5.631	ALA-292(3.35Å),	THR-302(4.72Å),	THR-315(3.01Å), CYS-291(3.32Å), SER-36(3.67Å)

Table 4.

The electronic excitations, transition energies (ΔE), oscillator strength (f_o), transition moment (μ_{ng}), % configuration interaction (C.I.) and change in dipole moments between ground and crucial excited states ($\Delta\mu_{ng}$) for all compounds at TD-M06/6-311G* level of theory

Sys.	Electronic Excitation	ΔE (eV)	f_o	μ_{ng}	Transition	%C.I.
ligand	$S_0 \rightarrow S_9$	4.710	0.340	0.865	H-1 $\rightarrow$ L+1	47
(1)	$S_0 \rightarrow S_5$	3.962	0.356	1.891	H-3 $\rightarrow$ L	63
(2)	$S_0 \rightarrow S_9$	4.708	0.287	1.500	H-1 $\rightarrow$ L+1	50
(3)	$S_0 \rightarrow S_{10}$	4.779	0.60	1.991	H-2 $\rightarrow$ L+1	58

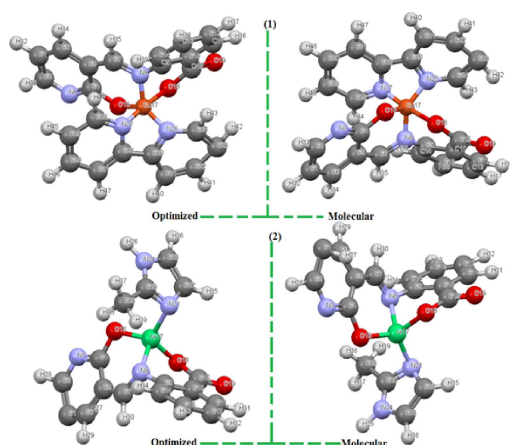


Figure 1. Optimized and molecular structures of a Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) with atom numbering scheme derived from DFT method.

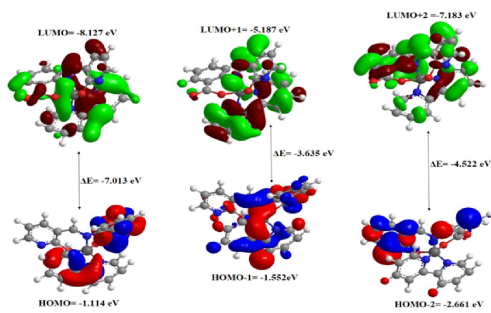


Figure 2. Frontier molecular orbitals of a Cu(II) complex [Cu(L)(bipy)] (1).

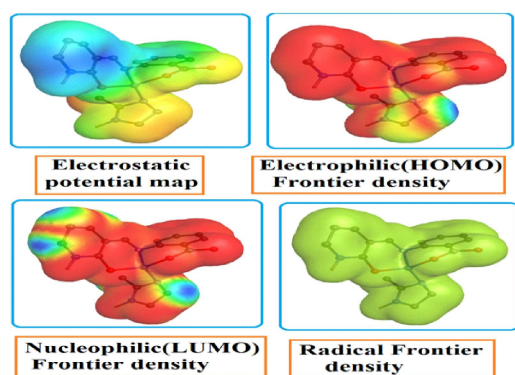


Figure 5. Electrostatic potential maps of a Ni(II) complex [Ni(L)(Me-ImH)] (2).

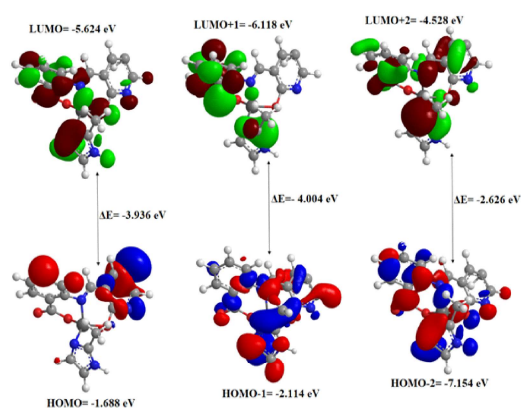


Figure 3. Frontier molecular orbitals of a Ni(II) complex [Ni(L)(Me-ImH)] (2).

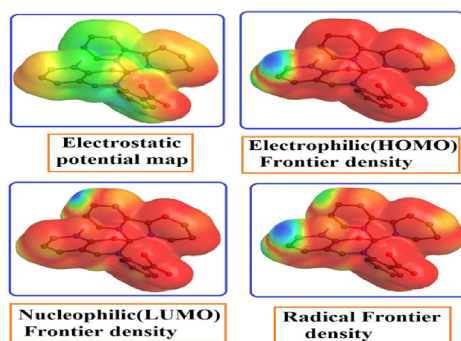


Figure 4. Electrostatic potential maps of a Cu(II) complex [Cu(L)(bipy)] (1).

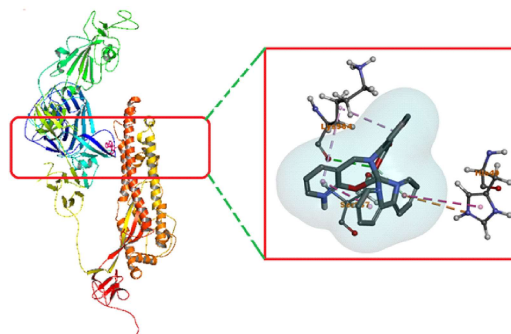


Figure 6. The docked Cu(II) complex [Cu(L)(bipy)] (1) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues around the docked complex.

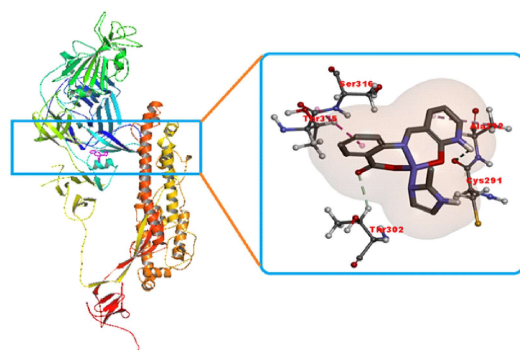


Figure 7. The docked Ni(II) complex [Ni(L)(Me-ImH)] (2) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues around the docked complex.

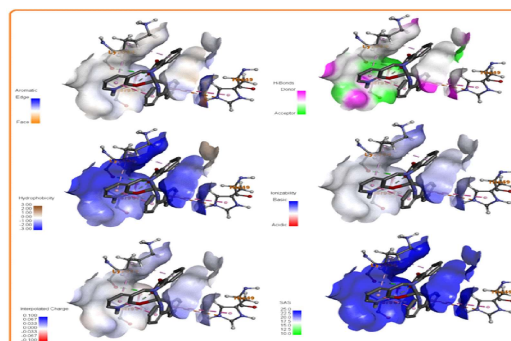


Figure 8. The representation of a docked Cu(II) complex [Cu(L)(bipy)] (1) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues.

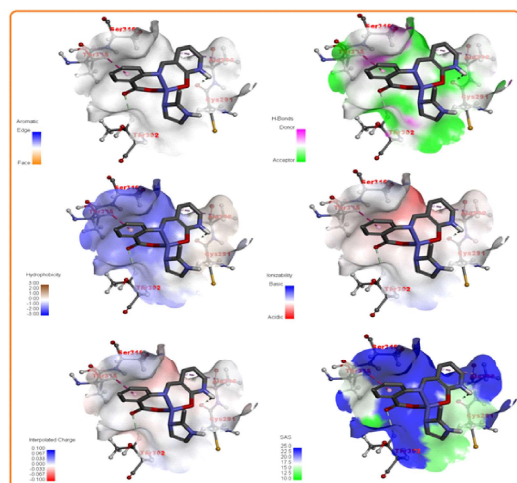


Figure 9. The representation of a docked Ni(II) complex [Ni(L)(Me-ImH)] (2) inside the M^{pro} protein (PDB ID: 7DWY) with its focused view for interacting residues.

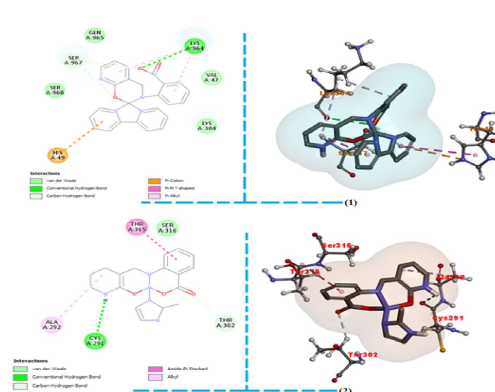


Figure 10. A Cu(II) complex [Cu(L)(bipy)] (1) and a Ni(II) complex [Ni(L)(Me-ImH)] (2) is docked into the binding cavity of the receptor protein interaction of SARS-CoV-2 M^{pro} (PDB ID: 7DWY); The molecular re-docking study showed in surface view and 3D protein backbone with ligand (complexes) represented as a cartoon and corresponding 2D complex interaction plot.

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