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Copper (II) complex [Cu(L) (IMD)].H₂O: synthesis, spectral, molecular structural investigations, FMOs, and *Insilco* biological assets

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Abstract
In this article, we report the experimental and theoretical chemistry of the copper(II) complex. The complex was synthesized by treatment of $CuCl_2.2H_2O$ with ONO-donor Schiff base and imidazole in equimolar molar amounts in methanol to produced [Cu(L)(imd)].H₂O 1 [where H₂L=2-Hydroxynapthaldehyde-N-isonicotinic acid hydrazide. The synthesized ligand as well as the complex were characterized by physicochemical techniques like magnetic measurements, infrared, electronic, and ESI-Mass spectral methods. The square planar geometry for Cu(II) complex 1 has been assigned with (3+1) coordination environments, HOMO-LUMO, and its energy gap was done with the DFT approach. Moreover, ligands and complexes were also exposed to Insilco drug-likeness and bioactivity score prediction by Molinspiration software.

Keywords: Copper (II), experimental, theoretical, and spectroscopy

Introduction

Transition metal complexes with Schiff base ligands containing a carboxylate group have been of great interest due to their application as essentially biologically active (Whitener *et al.* 1999; Young *et al.* 1995) [34, 35]. In this area, transition metal complexes, particularly Cu(II) complexes, have been investigated widely (Lefebvre *et al.* 2004) [17]. For Cu (II) ion, the coordination number varies from 4 to 6, the d9 configuration is Jahn–Teller active, and there is one odd d-electron occupies in one of the d-orbitals which gives rise to structural flexibility (Zhou *et al.* 2007) [36] and ability to form bonds with different donors simultaneously (Zhou *et al.* 2007) [37]. Copper (II) ion is one of the most important transition metal ions studied because of its involvement in a large number of biological processes like respiration, iron transport, oxidative stress protection, blood clotting, and pigmentation (Arnesano *et al.* 2004) [2]. Schiff bases are important intermediates for the synthesis of some bioactive compounds (Venturini *et al.* 2002; Delpiccolo *et al.* 2002) [31, 7]. 2-Hydroxy-1-naphthaldehyde has been proposed previously as a derivatization reagent for hydrazine and isoniazid determination in aqueous solution and isoniazid and hydrazine in plasma. 2-Hydroxy-1-naphthaldehyde as such and as Schiff chelating molecules is well-documented (Manes *et al.* 1990; Miralles *et al.* 1993) [19, 23] in coordination chemistry. Like several drugs, Imidazole and its derivatives are very important from a biological point of view (Pierre *et al.* 1995) [28], Benzimidazole is an important compound involved in a variety of biological processes, their antibacterial and fungicide activities are well known (Valdez *et al.* 2002) [30]. Benzimidazole compounds possess an extensive range of biological actions, such as antiphrastic and antitumor (Ramla *et al.* 2006; Catalán *et al.* 2010; Dobrzyn´ska *et al.* 2010) [29, 6, 11].

Density functional theory calculations (DFT) are an important tool providing insights into the properties of species that may arise in metal/ligand aqueous systems (Becke *et al.* 1986; Perdew *et al.* 1996; Koster *et al.* 2004) [4, 27, 16]. The four main approaches for calculating molecular properties are semi-empirical, *ab*-initio, density functional theory (DFT), and molecular mechanics (MM) methods. These quantum chemical methods can provide information regarding vibration modes, molecular geometry, ionization potential, the heat of formation, force constant, electron density, dipole moments, population analysis, conformation analysis, chemical reaction pathways, thermodynamic properties, etc. Though, semi-empirical methods are not so accurate methods these serve the purpose of approximate calculation of different chemical properties (Kishor *et al.* 2002; Dewar. *al.* 1977; Maurya *et al.* 2015) [15, 8, 20].

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In the present work, DFT calculations have been performed for the species formed from the interaction of Cu^{2+} ion with ONO donor Schiff base and imidazole ligand. The geometrical, and electronic properties of the different species of Cu^{2+} are presented and discussed. The organic ligand 2-hydroxy-1-napthaldehyde (HL), is a good ketonic compound which is reacted with the isonicotinic acid hydrazide amine (HL) group which was used as an ONO donor ligand, and as a neutral nitrogen donor substituted imidazole ligand. Moreover, in silico biological screening was dome in this paper.

Experimental
Materials and Methods: Copper(II) chloride dihydrate (BDH, Chemicals, Bombay), 2-Hydroxy-1-naphthaldehyde (Fluka AG Co., Switzerland), Isonicotinic acid hydrazide and Imidazole (Thomas Baker, Mumbai) ethanol (Bengal Chemical and Pharmaceuticals Ltd., Kolkata) was used as purchased. All chemicals used in this work were of analytical reagent grade. Elemental analysis was performed on an Elemental Vario ELIII Carlo Erba 1108 analyzer and ESI-Mass was recorded on a Jeol SX-102/DA 6000 mass spectrometer using xenon (6 kV, 10 mA) from CDRI, Lucknow. The magnetic susceptibility data were recorded on a Gouy balance at room temperature using mercury (II) tetrathiocyanato cobaltate (II) (χg = 16.44 x10-6 cgs unit) as the calibrate. The IR spectra (400–4000 cm^{-1}) were recorded on Bruker-αT, FT-IR spectrophotometer, with samples prepared as KBr pellets. Electronic spectra were obtained through Varian UV-Vis. spectrophotometer in quartz cells. The EPR spectrum was recorded at liquid nitrogen temperature (77 K) on a JES-FA Series EPR spectrometer and TGA from SAIF, IIT Bombay.
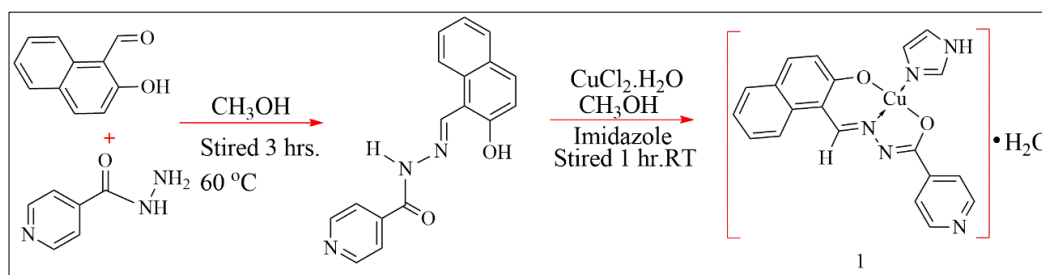
Synthesis of Schiff base: The Schiff base (4Z, N'E)-N'-((2-hydroxynaphthalen-1-yl) methylene) isonicotinohydrazonic acid: A solution of 2-hydroxy-1-napthaldehyde (0.344 g,

0.02M) in ethanol (10 mL) was added to a solution of isonicotinic acid hydrazide (0.274 g, 0.02M) in ethanol (20 mL). The mixture was stirred with refluxed for 4 hrs at 60 °C. The characteristic orange precipitate obtained by Schiff base condensation was filtered out and kept for slow evaporation at room temperature was characterized. Melting point: 240 °C. Anal. Calc. for $C_{17}H_{13}N_3O_2$ (MW: 291.10): C, 70.09; H, 4.50; N, 14.42, Found: C, 71.03; H, 4.56; N, 13.89 %. Solubility: Methanol, Acetonitrile, DMF and DMSO.

Synthesis of [Cu(L)(imd)].H₂O 1: The copper complex was prepared by the addition of a methanolic solution of H₂L (0.01 M, 0.291 gm) to a warm solution of $CuCl_2 \cdot 2H_2O$ (0.170 g) in 1 mL of water and 10 mL of methanol and maintain pH by addition of potassium hydroxide and stirring the solution at 25 °C for 30 min. added imidazole (1) (0.01M, 0.068 g dissolved in 10 ml methanol and stirred the solution at RT for 30 min. The brownish-colored solid, which separated on cooling, was filtered, washed with methanol water, and dried in vaccuo. Melting point: 270 °C. Anal. Calc. for $C_{20}H_{15}N_5O_2Cu$ (MW: 420.91): C, 57.95; H, 3.86; N, 15.72, Found: C, 57.07; H, 3.59; N, 16.64 %. Solubility: Methanol, Acetonitrile, DMF and DMSO.

Results and Discussion
The ONO donor Schiff base (4Z,N'E)-N'-(2-hydroxynaphthalen-1-yl)methylene)-isonicotinohydrazonic acid (H₂L) and their copper (II) complex 1 in current work was prepared according to the following Scheme: 1. Some physical properties of ligand and complex are given in Table 1. The complex is found to be stable in air and it is insoluble in most of the common organic solvents but it is soluble in DMF and DMSO. The compounds were characterized by elemental analysis, infrared, ESI-Mass, and electronic spectral studies, and magnetic and conductance measurements were also done.

Scheme 1: Synthetic route of Schiff base and complex 1.

Spectral analysis: The ONO donor Schiff base: (4Z,N'E)-N'-((2-hydroxynaphthalen-1-yl)methylene)-isonicotinohydrazonic acid H₂L contains three donor sites: (i) the phenol oxygen (ii) the azomethine nitrogen, (iii) the enolic oxygen of hydrazide these are suitable for chelation with metals. The experimental and computed IR spectrum of ligand shows in (Fig. 1) it shows bands at 3424, [3100-2800], 1696, 1586, 1528 and 1354 cm^{-1} assignable to ν(OH) (phenolic), [ν(CH), δ(CH)+, δad (CH₃) (in-plane bending asymmetric deformation), δ(CH) and γ(CH) (out-of-plane bending),] ν(C=O), ν(C=N), ν(C=C) and ν(C-O) respectively. This is further supported by the low energy shift [22] of ν(C-O) and appears at 1190 cm^{-1} in the complex compared to ν(C-

O) (phenolic) at 1354 cm^{-1} in the free (2-hndH). The coordination of carbonyl oxygen of the amide group in the ligand is enolized in the complex and a peak appeared at 1334 cm^{-1} of ν(C-O) mode in the complex compared to ν(C=O) of the ligand at 1696 cm^{-1} (Fig 2) The presence of coordinated/lattice water at 3420 and 3299 cm^{-1} indicated by the presence of ν(OH) modes. The non-ligand band occurring at 527 cm^{-1}, has been assigned to the ν(Cu-O) mode (Maurya et al. 2003) [21]. The good correlation between the experimental and theoretical vibrational frequencies was examined. Some slight variance in the experimental and theoretical frequencies might be due to the polarization, computation effects, and experimental conditions.
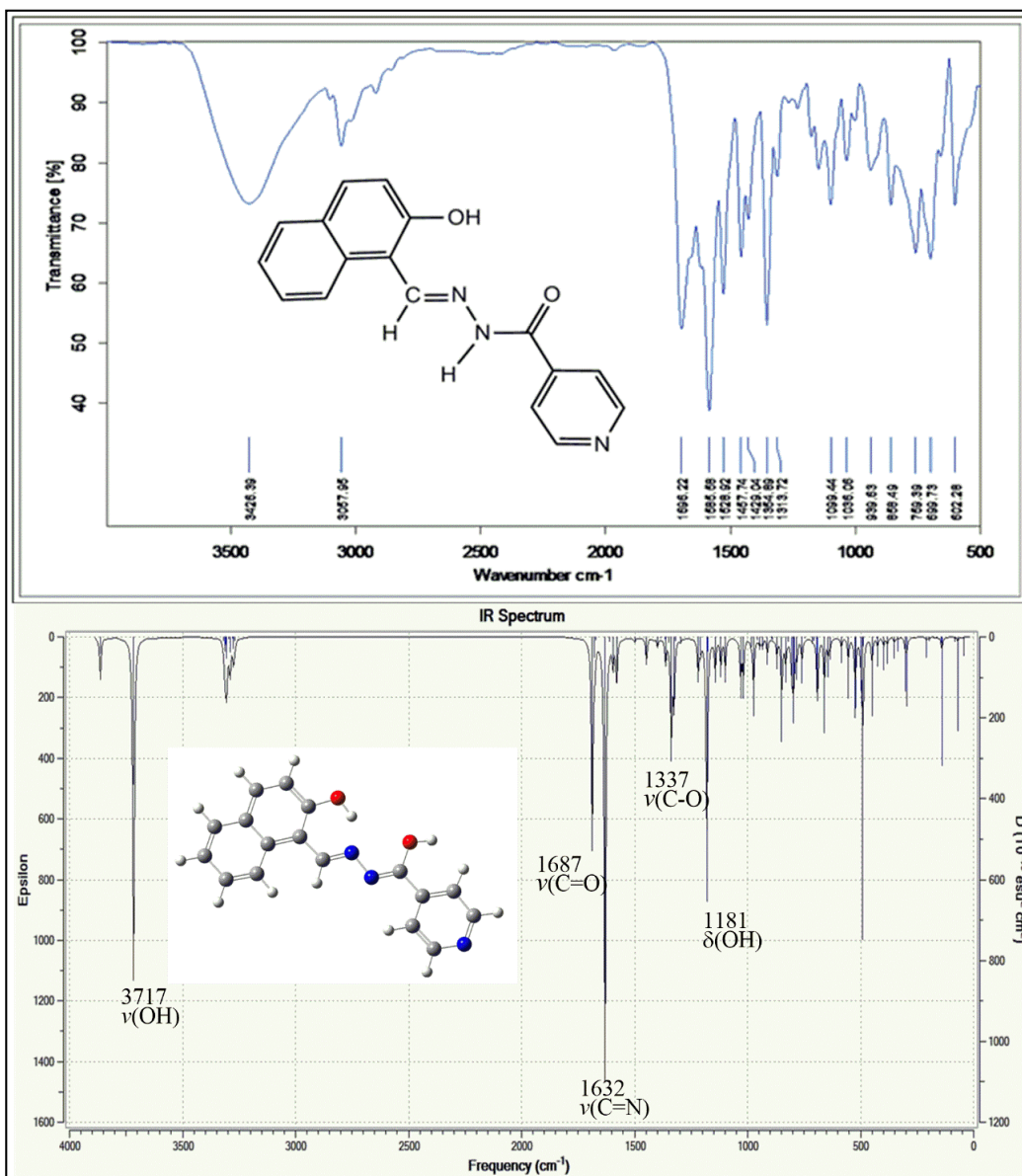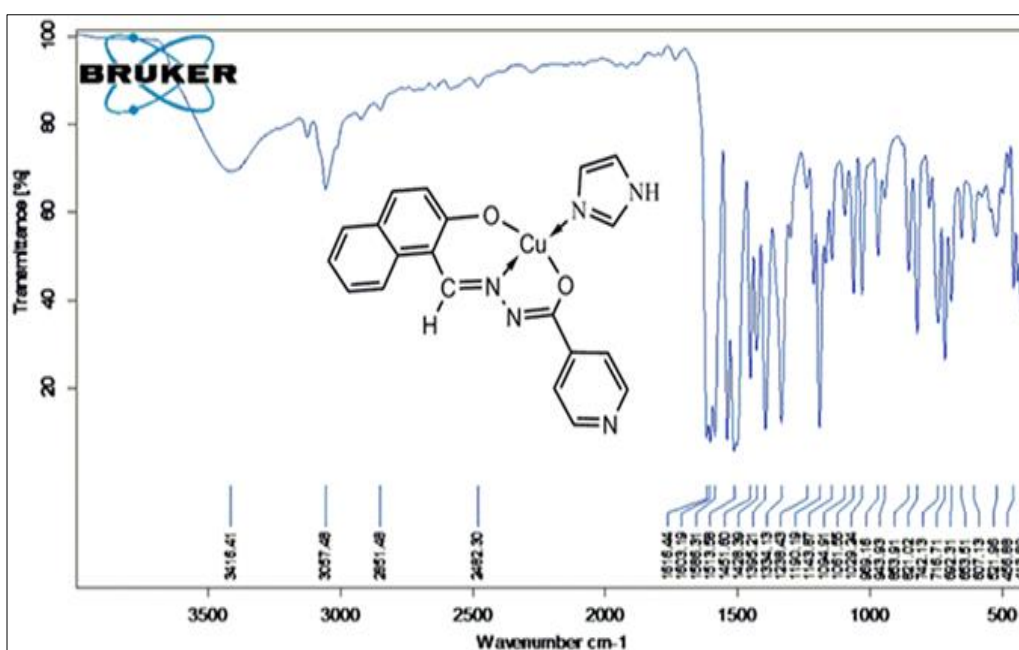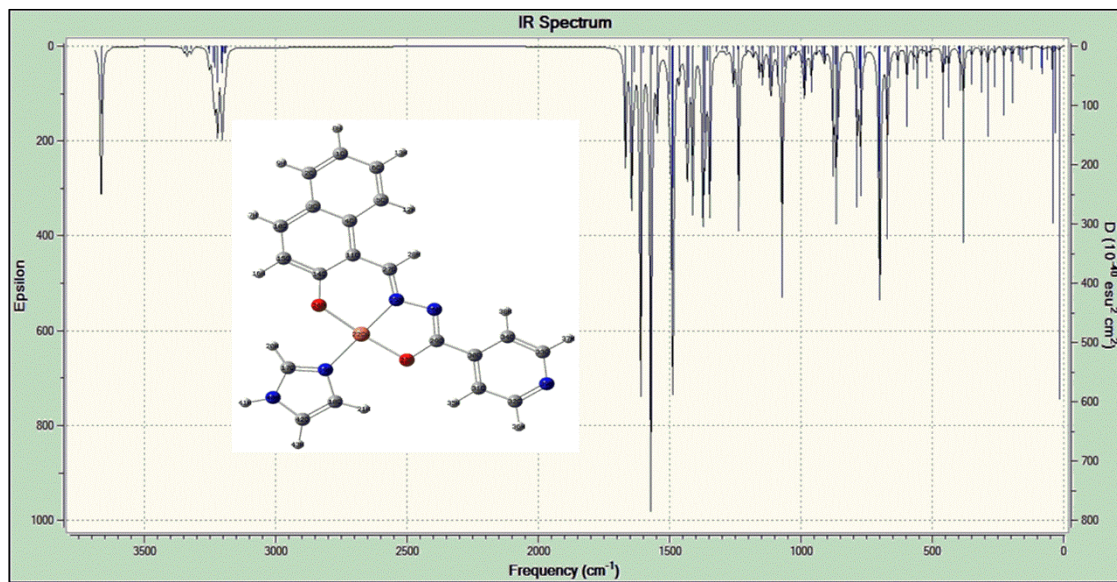
Fig 1: Experimental (upper) and Theoretical (lower) IR spectrum of H₂L.

Fig 2: Experimental (upper) and Theoretical (lower) IR spectrum of [Cu(L)(imd)].H$_2$O

The electronic spectrum of [Cu(L)(imd)].H$_2$O **1** was recorded in 10^{-3} M in methanol. The compound displayed three spectral peaks at 220, 349, and 636. The first two peaks may be assigned as charge transfer transitions, while the third peaks at 636 may be due to d-d transitions. The electronic spectrum of compound 1 is given in Figure 3. The mass spectrum of [Cu(L)(imd)].H$_2$O 1 is shown in Figure 4. The spectral peaks observed at 279, 175, and 138 m/z are most probably due to the following types of ion fragments:

[Molecular ion]$^+$ (420) – [imd] (68) - [C$_5$H$_5$N]$^+$ (78) = 275 + 4[H]$^+$ = 279

[2-hnd]$^+$ (172) + 3[H]+ = 175

[inah]$^+$ (137) + 1[H]+ = 138

These results are consistent with the proposed molecular composition of complex 1.
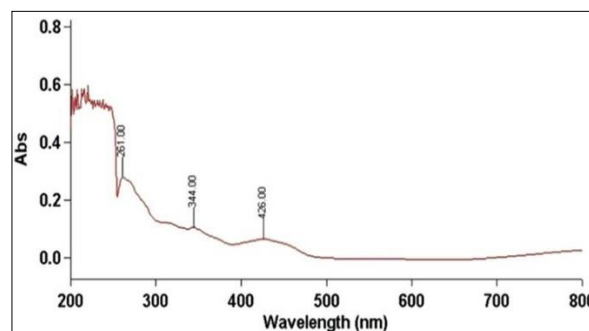
Fig 3: Experimental UV spectrum of complex [Cu(L)(imd)].H$_2$O
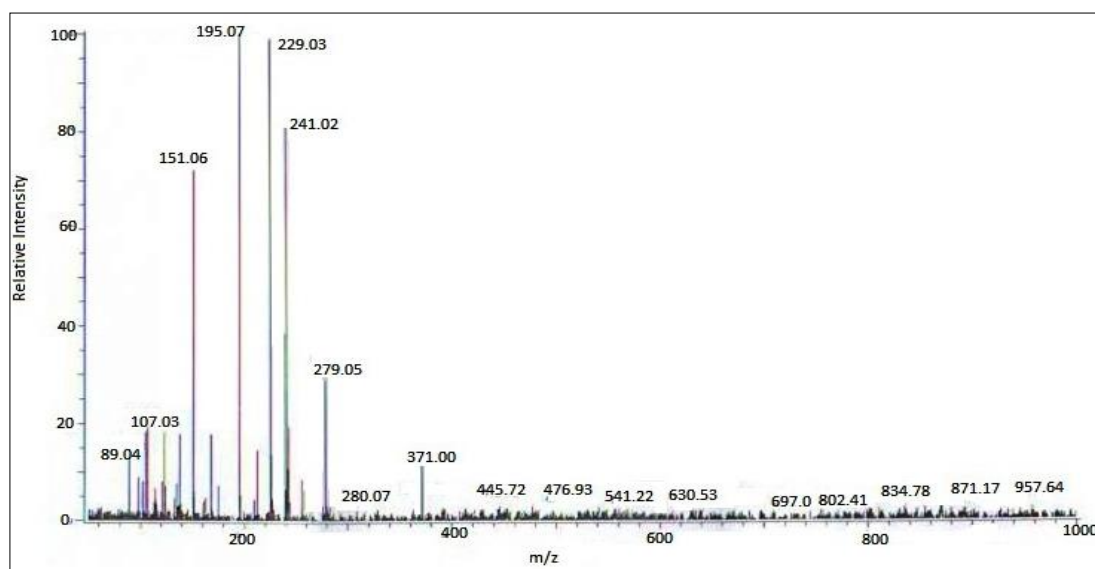
Fig 4: ESI-Mass spectrum of [Cu(L)(imd)].H$_2$O

Figure 5, depicted the X-band EPR spectrum of [Cu(L)(imd)].H$_2$O 1 at liquid nitrogen temperature (LNT) was recorded on the powdered sample at the microwave frequency 9.1 G.Hz., using DMSO as a solvent. The parallel feature of ^{63}Cu is not resolved in the spectra of the given compounds. The calculation of gav parameter for the compound is given below. The observed gav value of 2.037, which is less than

2.3, suggests the covalent nature of metal-ligand bonds in the compound (Maurya *et al.* 2003) [22].

Conductance measurements: The molar conductivity of complex in 10-3 M DMF solution lies at 11.7 ohm-1 cm^2 mol-1 as expected for non-electrolyte in nature. Such a non-zero molar conductance value of the complex in the present is most

probably due to the strong donor capacity of DMF, which may lead to the displacement of anionic ligand and change of electrolyte type (Patel *et al.* 1990) [25].
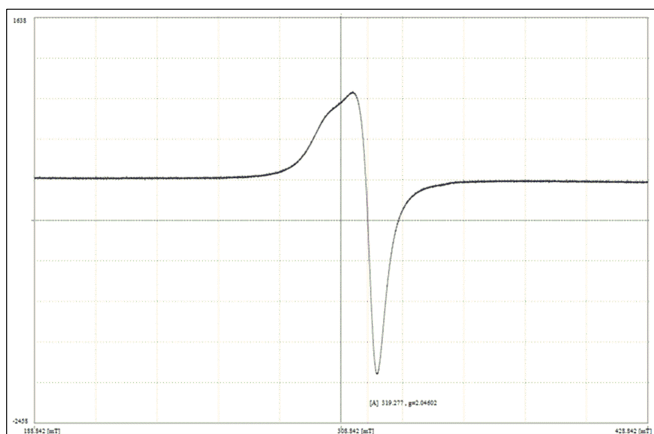

Fig 5: ESR Spectrum of Complex [Cu(L)(imd)].H$_2$O 1

Theoretical Calculations

Theoretical Chemistry: Theoretical chemistry was done with the density functional theory (DFT) approach (Frisch *et al.* 2010) [12]. To examine the molecular structure, vibrational properties, and FMOs of the studied ligand and its complex with B3LYP/6-311+G and B3LYP/LANL2DZ combinations. The assignment of the computed frequency was supported through the Gauss View 5.0 graphical interface for the Gaussian program, which gives a pictorial presentation of the shape of the vibrational modes (Bayari *et al.* 2005) [3]. The energies of FMOs were used to define molecular stability (Parte *et al.* 2021) [24]. With the object to obtain a deeper understanding of the interaction between copper metal ions with the O$_2$N$_2$ environment, ab initio total-energy calculations within the density functional theory (DFT) framework were carried out for (4Z,N'E)-N'-((2-hydroxynaphthalen-1-yl)methylene)isonicotinohydrazonic acid and its complex.

Molecular structural framework: The molecular structure study of [Cu(L)(imd)].H$_2$O 1 was optimized using the Density Functional Theory (DFT) approach through Gaussian 09 software. The computed interatomic distances, around the metal center, are as, Cu-O$_{(24)}$; 1.927 Å (enolic oxygen of 2-hydroxynepthaldehyde) Cu-O$_{(23)}$; 1.965 (enolic oxygen of isonicotinic acid hydrazide) Cu-N$_{(25)}$; 1.981 (azomethine nitrogen) and Cu-N$_{(19)}$;1.963 (nitrogen of imidazole) were observed. The significant selected computed bond angles are as, O$_{(23)}$-Cu-O$_{(24)}$; 164.45°, O$_{(23)}$-Cu-N$_{(25)}$; 82.24°, O$_{(24)}$-Cu-N$_{(25)}$; 88.49°, N$_{(19)}$-Cu-O$_{(23)}$; 97.43°, N$_{(19)}$-Cu-O$_{(24)}$; 94.93° and N$_{(19)}$-Cu-O$_{(25)}$; 163.77° these geometrical data suggested the distorted square planner geometry with (3+1) coordination

environments with ONO donor Schiff base and imidazole ligands. These results are comparable to single crystal structural data reported (Patel *et al.* 2008) [26] in the same environments. The computed optimized structure of the complex [Cu(L)(imd)].H$_2$O 1 is shown in Fig. 6.
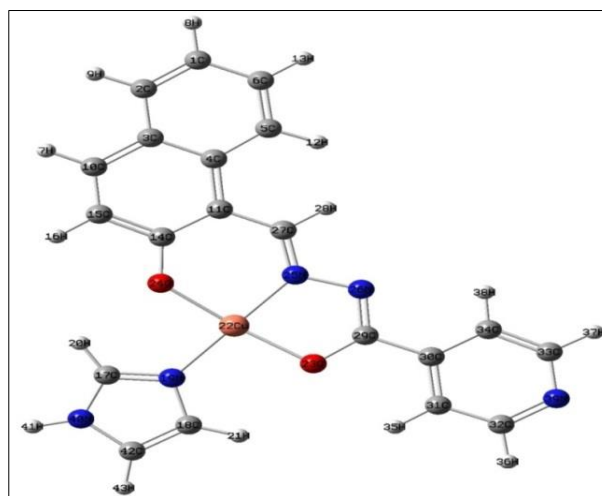

Fig 6: Optimized Structure of Complex [Cu(L)(imd)] 1.

Frontier molecular orbital analysis: The chemistry of FMOs (HOMOs and LUMOs) are very important parameters (Vishwakarma *et al.* 2022) [33] for chemical reactions. One can determine the way the molecule interacts with other species. Hence, they are called Frontier orbitals. The HOMO is the orbital that primarily acts as an electron donor and the LUMO is the orbital that largely acts as the electron acceptor, and the gap between HOMO and LUMO characterizes the molecular chemical stability (Fukui *et al.* 1982) [13]. Here we selected the four significant molecular orbitals (MOs), *viz.*, [HOMO-1], [HOMO], [LUMO] and [LUMO+1] are worked out for the Schiff base are -7.108, -6.719, -0.683, -0.674, and -0.624 eV respectively. The energy gap (ΔE) between HOMO-LUMO; 6.063 HOMO-1-LUMO+1, 6.433 eV. While the computed energies of [Cu(L)(imd)].H$_2$O **1** in the same order are as -6.232, -5.397, -2.041, -1.122, eV and energy gap between [HOMO-LUMO]; 3.357 and [HOMO-1–LUMO+1]; 5.111 eV. The electronic insides of MOs of ligands are due to paired electrons in the HOMO justifies that it is diamagnetic nature. While its paramagnetic nature is concerning one unpaired electron in HOMO. Thus, the HOMO in the complex may be labeled as a singly occupied molecular orbital (SOMO). The energy of the frontier orbitals for molecules in terms of ionization energy (IE) and electron affinity (EA) of the 2-hydroxy-N'-(1-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl) ethylidene) benzohydrazonic acid and its complex from Koopmans's theorem (Brabec *et al.* 2001) [5].
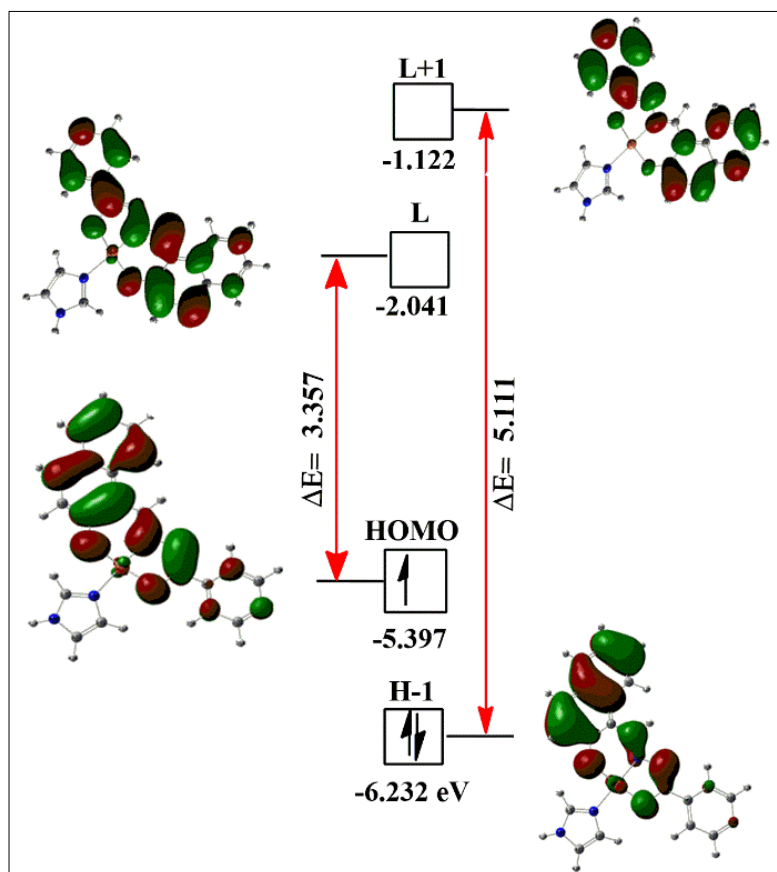
Fig 7: HOMO(H)-LUMO(L) cantor plot with energy and their energy gap in eV of 1.

Bioactivity ranking Prediction of drug-likeness properties:
The pharmacological activity of pharmaceuticals is defined by its highly applicable interaction with a variety of biological targets including enzymes, ion channels, and receptors in living things. The bioavailability of the studied compounds was predicted by subjecting them to calculations through the web server, www.molinspiration.com, and the results are shown in Table 1. The bioactivity scores are monitored based on parameters like, (i) G-protein coupled receptor ligand (GPCRL), (ii) ion channel modulation (ICM), (iii) nuclear receptor ligand (NRL), (iv) protease inhibition (PI), (v) enzyme inhibition (EI), According to some research, substances with bioactivity scores of 0.0 or higher are extremely bioactive, while those with scores of 5.0 to 0 have moderate activity, and those with a score of 5.0 or above are inactive (Verma *et al*. 2012) [32]. The present studied compounds have values of -0.67 to 0.07, so they are expected to have moderate activity (Dhanraj *et al*. 2016) [9]. The scores are charted in Table 1. These are predictable to retain such properties as demand for them to behave as potential drugs with some alterations in their molecular structure (Khan *et al*. 2017) [14].

Lipinski's rule: A benchmark for drug design and development, Lipinski's rule of five (RO5) helps in the description of molecular characteristics of drug candidates that gave insight into many pharmacokinetic parameters, including absorption, distribution, metabolism, and excretion (ADME), for predicting the success of an orally administered drug's journey through the body to the site of action. About a certain molecular characteristic, (i) logP (partition coefficient), (ii) molecular weight, (iii) number of hydrogen bond acceptors, (iv) hydrogen bond donors, and (v) polar surface area, the rule predicts the oral activity of a drug candidate. A drug candidate for an orally active medication should contain logP (≤5), hydrogen bond acceptors (≤10), hydrogen bond donors (≤5), and a molecular weight of (≤500), according to RO5 (Lipinski *et al*. 2001) [18]. An orally active medicine shouldn't typically exhibit any rule violations. Here, the data for the investigated compound's molecular weight, TPSA, milLogP, and other parameters are computed and plotted in Table 2. Under Lipinski's Rule (Ammal *et al*. 2016) [1], it can be shown that ligand H₂L and complex 1 have milLogP values of 2.59 and -5.16, respectively, which are within the acceptable range for a drug candidate to pass through bio-membranes and exhibit good bioavailability. The ligand and its Cu(II) complex do not exhibit any Lipinski's rule violations. for the investigated compounds to qualify as oral therapeutic molecules under RO5. However, the most recent advancements in drug discovery have expanded the chemical space for candidates that are orally druggable beyond Lipinski's rule. So, the studied compounds can be considered oral therapeutic molecules as per RO5. But the recent developments in drug discovery have increased the chemical space for oral druggable candidates beyond Lipinski's Rule of 5 (bRo5) by considering target interaction and incorporating various natural products rich in activities (Doak B C, *et al*.) [10].

**Table 1:** Bioactivity score of the ligand and its complex.

Comp.	Parameters of Bioactivity score					
	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear recepto ligand	Protease inhibitor	Enzyme inhibitor
H$_2$L	-0.31	-0.67	-0.27	-0.48	-0.48	-0.30
1	0.11	0.06	-0.06	-0.41	0.07	0.34

Table 2: Drug-likeness score of the ligand and its complex.

Comp.	Lipinski's Parameters						
	% Abs.	TPSA (Å)^2	MlogP	nOHNH	nON	nrtb	Lipinski's violations
H$_2$L	83.24	74.58	2.91	2	5	3	0
1	86.09	66.41	-5.16	1	7	2	0

Percentage absorption was calculated by % Absorption = 109-[0.345×Topological Polar Surface Area] Topological polar surface area (defined as a sum of surfaces of polar atoms in a molecule), Logarithm of compound partition coefficient between n-octanol and water, Hydrogen bond donors (nOHNH), Hydrogen bond acceptors (nON) and Number of rotatable bonds (nrotb).
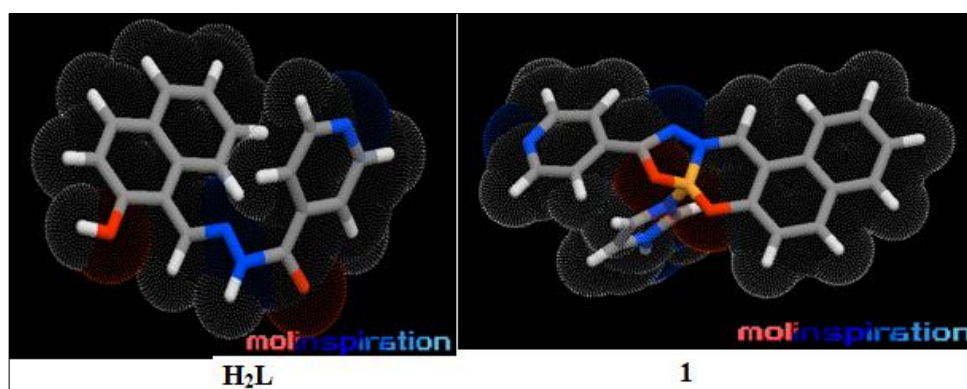
Fig 8: 3D-Molecular structures of ligand (H$_2$L) and their complex **1** obtained through Molinspiration galaxy 3D structure generator v2021.01 beta a web-tool.

Conclusion
The satisfactory analytical data coupled with the studies presented above indicate that the complex under this investigation is of general composition, [Cu(L)(imd)].H$_2$O [where H$_2$L=2-hydroxy-1-naphthaldehyde-N-isonicotinic acid hydrazide and imidazole (imd). The complex so obtained has been characterized based on elemental analyses, molar conductance and magnetic measurements, mass, electron paramagnetic resonance, and infrared and electronic spectral studies. Suitable square plane structures have been proposed for the complex. The 3D molecular modeling and analysis for bond lengths and bond angles have also been carried out for one of [Cu(L)(imd)].H$_2$O 1 to substantiate the proposed structure. Insilco biological screening indicates that the studied ligand and its complex are good drug candidates possessing diverse biological activities.

Acknowledgments

Author contributions
PKV: Synthesis work, data collection, theoretical work, and writing manuscript. RCM: research plan final drafting manuscript. The authors contributed to the article and approved the submitted version.

Disclosure statement
The authors declared that no war of interest with this work.

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