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Synthesis, characterization and DFT studies of Schiff base (E)-4-(((5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene) amino)-benzenesulfonamide and its MoO_2 (II) complex

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Abstract
This research article reports the experimental and theoretical model of the synthesised ligand (E)-4-(((5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene) amino) benzenesulfonamide (HL) and their complex *cis*-$[MoO_2(L)_2]$ {1}. The physicochemical, spectral, and theoretical results proposed the molecular formula of the complex as cis-$[MoO_2(L)_2]$ (where L = monobasic bidentate ligand of 4-formyl-3-methyl-1-phenyl-2-pyrazoline-5-one with sulfanilamide**.** The colored solid mass was grown, washed with ethanol, and dried in air. The complex is soluble in inorganic solvent like DMF and DMSO and organic solvents like methanol, ethanol, and acetonitrile. The computed results like geometry, molecular orbital analysis and NLO properties done via DFT approach. The computed geometrical results have determined the molecular structure of the compound. It has been shaped that the ligand coordinates via azomethine nitrogen and enolic oxygen of Schiff base moiety, by a 1:2 metal-ligand ratio. Furthermore, the title compounds were also showing Insilco bioactivity score and drug-likeness by molinspiration software and ADME properties resulted pharmacological action of the compounds.

Keywords: Synthesis, characterization, DMSO, NLO, DFT

Introduction
The chemistry of sulfa drug derived Schiff bases have been shown to possess well-pronounced biological implications and have led to considerable interest in their coordination chemistry. Sulfonamides are the first drugs to display potential for treating various diseases, have attracted interest in their coordination chemistry due to their broad-spectrum biological activity [1]. Due to the fascinating properties of organic sulfur molecules and have been found to be effective coordination compounds [2]. The Schiff base coordinated complexes of this form have been found to have catalytic significance in terms of both *in vivo* and *in vitro* experiments [3, 4]. The coordination chemistry of Mo (VI) is of interest to biological systems due to it vide biochemical significance [5, 6]. Several mono-nuclear molybdenum enzymes are often referred to as "oxomolybdenium" enzymes. Schiff base dioxido-molybdenum complexes are excellent enzyme model systems for the active sites of transferase enzymes like nitrate reductase, the active sites of which consist of a cis-MoO_2 moiety [7, 8]. In addition to the application of molybdenum(VI), Schiff base complexes possessing Mo=O in electrochemistry [9], Schiff base complexes derived from amino acids have attracted much attention because of their inorganic and biological importance [10, 11]. Quantum chemistry is a branch of theoretical chemistry that uses quantum mechanics and quantum field theory to study chemistry research. Recent years have seen the use of these methods in all aspects of drug development, providing new ways to design drugs and improve existing ones. This article introduces the fundamental principle and calculation methods used in quantum chemistry. Additionally, progress on using quantum chemistry techniques in different areas of pharmaceutical research was discussed [12].
In this work, we synthesized organic and inorganic moiety then computational based DFT calculations and ADME properties have been performed for the species produced through the interaction of *cis*-$[MoO_2]^{2+}$ ion with ON donor Schiff base ligand. The molecular geometrical and electronic properties are presented and discussed.

The 4-formyl-3-methyl-1-phenyl-2-pyrazoline-5-one (HL) is a good ketonic compound which is reacted with the sulfanilamide as amine group, which was used as an ON donor monoprotic ligand.

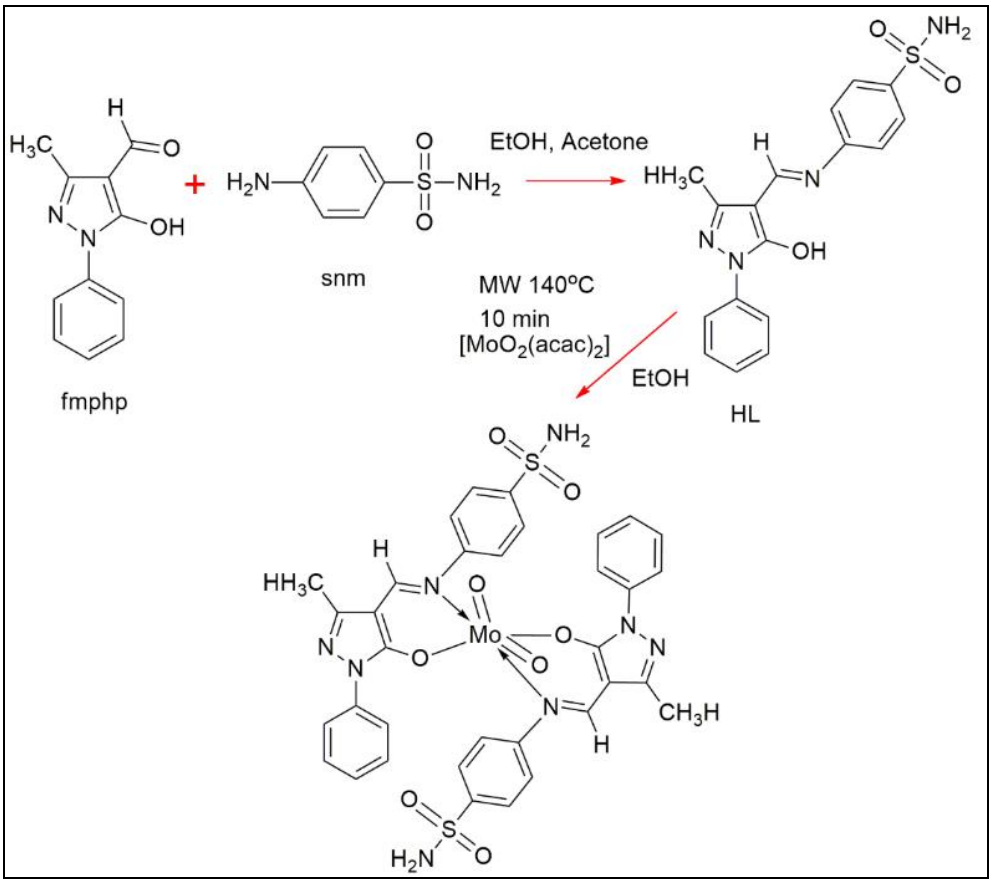
Experimental

Materials and Method: The chemicals used in this research work were of analytical reagent grade. Elemental analysis was obtained from CDRI. The IR spectra 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 from our department. DFT studied of compound HL and {1} were done at B3LYP/LANL2DZ level of theory by Gaussian 09 programme [13]. The insilco biological prediction like: Bioactivity prediction of drug-likeness properties were predicted by subjecting them to calculations through the web server, www.molinspiration.com. The ADME properties, including five parameters like absorption, distribution, metabolism, excretion, and toxicity, were predicted with the support of the ADMETSAR methodology [14] web server (http://lmmd.ecust.edu.cn/admetsar2).

Synthesis

Schiff base (HL): Methanolic solution of 4-formyl-3-methyl-1-phenyl-2-pyrazoline-5-one (1.020 g, 5 mmol) and sulfanilamide (0.860 g, 5 mmol) was taken in a round bottom flask in hot methanol-acetone (8:2) 10 ml solution was mixed, and the reaction mixture was refluxed for 5 h and then it was kept overnight at room temperature. The solid product was then filtered, washed with cold methanol, recrystallized from the same solvent then dried *in vacuo*.

$[MoO_2(L)_2]$ {1}: Complex was synthesized from microwave synthesis reactor mono wave-200, by the method described below. A 1:2 molar methanolic solution of $[MoO_2(acac)_2]$ (0.5 mmol, 0.164 g) and Schiff base HL (1 mmol, 0.353 g) were mixed in 30 ml vial then the reaction mixture was stirred for 10 min hrs at 140 ^{0}C dark yellow precipitate appeared. The precipitate was separated by vacuum filtration and washed with methanol. The solid mass was dried in air at room temperature and stored in a $CaCl_2$ desiccator.



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

Result and Discussions

The sulfa drug derived ON donor Schiff base E)-4-(((5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl) methylene) amino) benzenesulfonamide (HL) & their MoO_2(VI) complex {1} in current work was prepared according to the following Scheme 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, and electronic spectral studies, and electrochemistry were also done.

Spectral analysis: Infrared spectral data of the synthesized monoprotic Schiff base HL and their metal complex {1} are shown in Figures 1 and 2, respectively. The vibrational spectrum of HL it shows the three distinctive stretching vibration bands are observed as [3335,ν(OH)]; [3221,ν(NH)] and [1587, ν(C=N)] cm^{-1}. After the complexation, the spectral band of [ν(C=N), 1588 cm^{-1}] is shifted to a lower wavelength at ~1573 cm^{-1} in the metal

complex suggesting coordination through the azomethine group [19]. The band at 3419 cm^{-1} *ν*(OH) does not appear in the complex, confirming the metal-oxygen coordination. The IR spectra of cis-dioxidomolybdenum(VI) complex {1} express two bands at 928 and 868 cm^{-1} which are attributed to ν_{asymm}(O=Mo=O) and ν_{symm}(O=Mo=O) stretching vibration of cis-[MoO_2] structure [15].

The electronic spectra of HL and *cis*-MoO_2(VI) {1} were recorded in the DMSO solution are given in Figures 3 and 4. The ligand (HL) shows high-intensity absorption bands at 302 and 348 nm in the ultraviolet region can be attributed to π-π* and n-π* transitions or intra ligand charge transfer (ILCT) [16]. In the electronic spectrum of the studied {1}, the bands that appear at the UV region at 264 and 314 nm are due to the intra-ligand transitions and have been assigned as π–π* and n–π* transitions. Furthermore, an additional band of medium intensity at 412 nm can be assigned to a ligand to metal charge transfer (LMCT) band due to the transfer of charge from the filled p-orbital of the coordinated enolic oxygen atoms to vacant d-orbitals of the metal [17]. As Mo (VI)-complexes have $4d^0$ configuration, the d-d band is not expected.

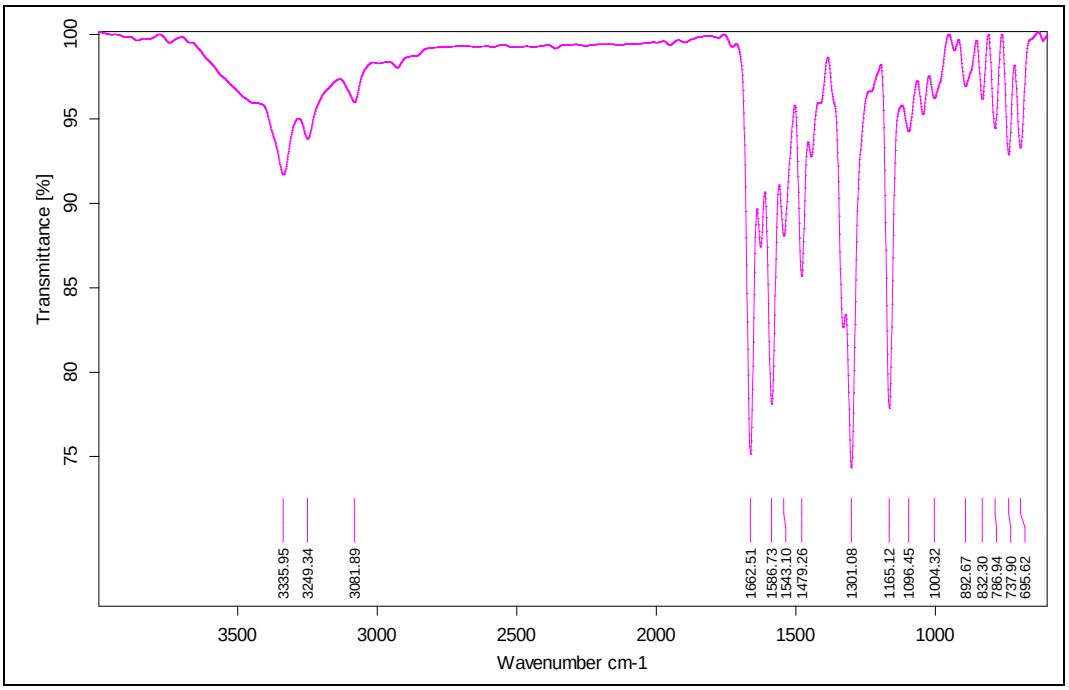


Fig 1: Infrared spectrum of the ligand HL.

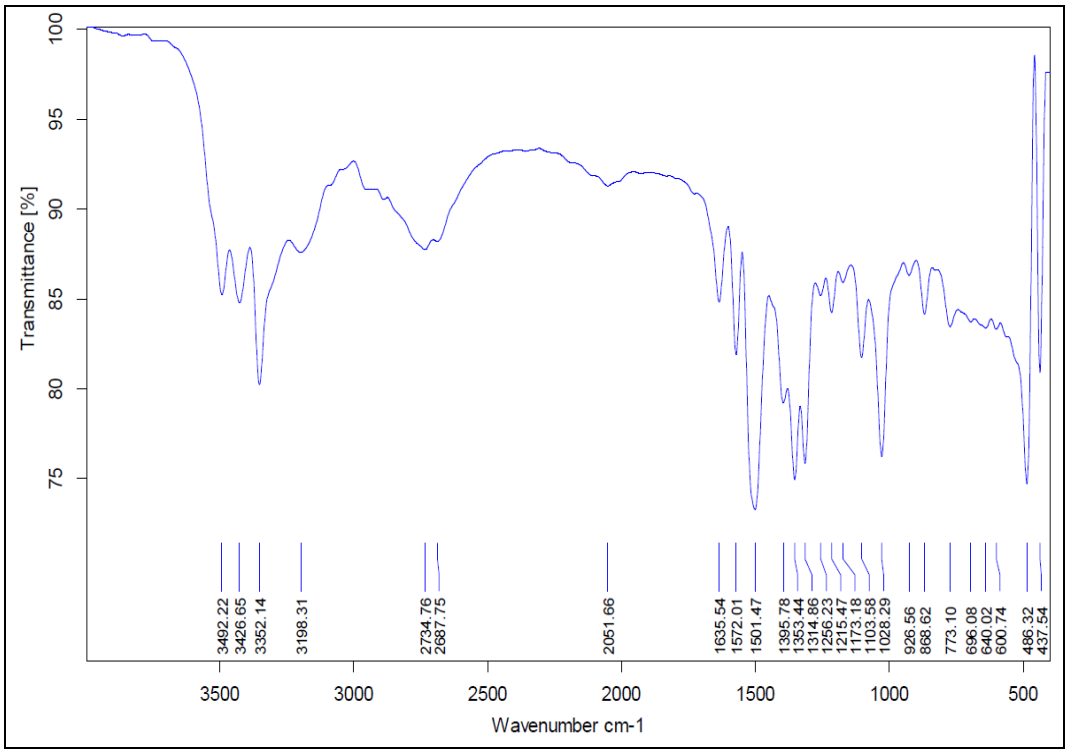


Fig 2: Infrared spectrum of *cis*-[$MoO_2(L)_2$] {**1**}.

Electrochemistry

The redox properties of the corresponding complex compound {1} was investigated through cyclic voltammetry in 100 mV/Sc scan range at Ag/AgCl in 0.1M solution of TBAP as supporting electrolyte. Figure 3, represented the voltammogram of $[MoO_2(L)]$ {1} is displayed in two steps an irreversible reduction peak as [E_{pc} (-0.752) V; I_{pc}(7.116) µA] and [E_{pc} (-0.780) V; I_{pc}(3.308) µA] that can be used to establish as $[MoO_2]^{2+} \rightarrow [MoO_2]^{+}$ and $[MoO_2]^{+} \rightarrow [MoO_2]$ and one step an irreversible oxidation wave as [E_{pa} (-0.622) V; I_{pa} (3.302) µA] that can be used to establish as $[MoO_2] \rightarrow [MoO_2]^{2+}$. Furthermore, the corresponding formal reduction potential Er is observed as -0.687 V. The peak current ratio Ipa/Ipc (0.50) is less than unity, showing that the electron transfer reaction is followed by a chemical reaction (EC mechanism) [27]. Additionally, the HOMO-LUMO energy gap (Eg) is calculated from the onset potential of electrochemical reduction and oxidation are given in Table 1. The molecule can be used in the optoelectronic device based on the HOMO LUMO energy band structure.

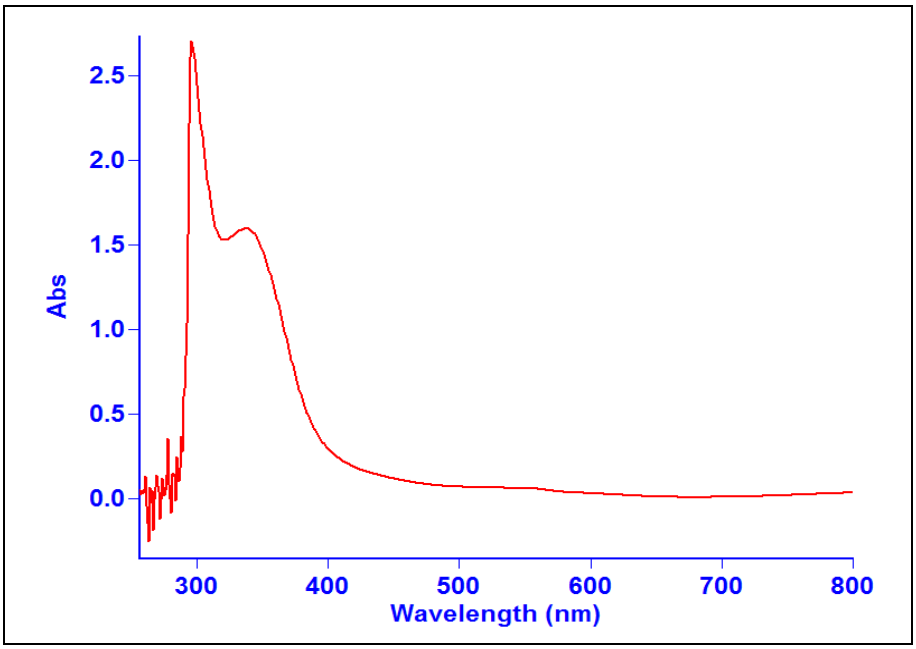


Fig 3: UV/Vis. spectrum of HL in 100 µM DMSO solution.

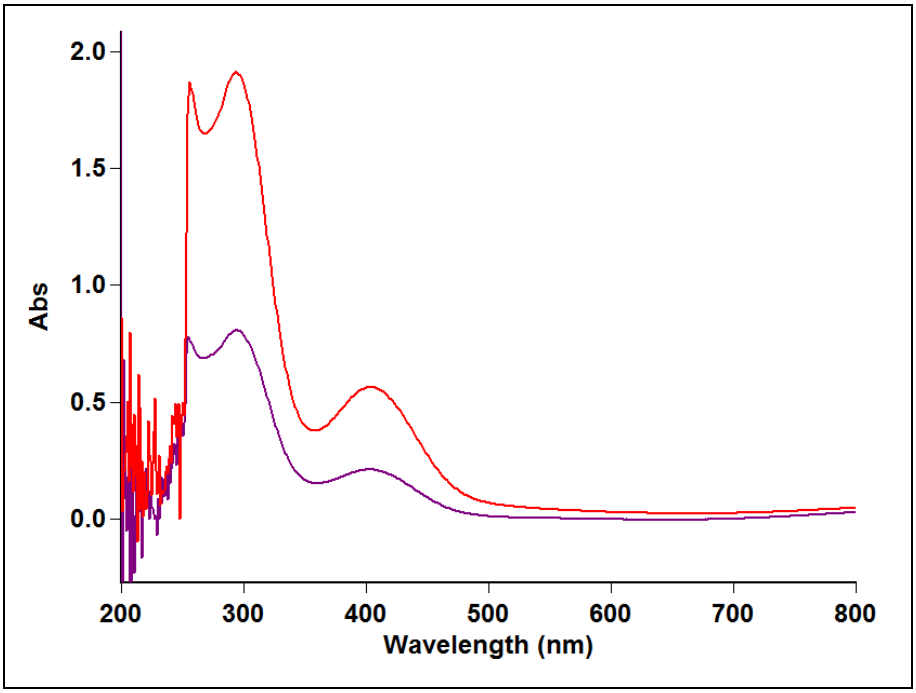


Fig 4: UV/Vis. spectra of $[MoO_2(L)_2]$ {1} in 50 (blue line) and 100 (red line) µM in DMSO.

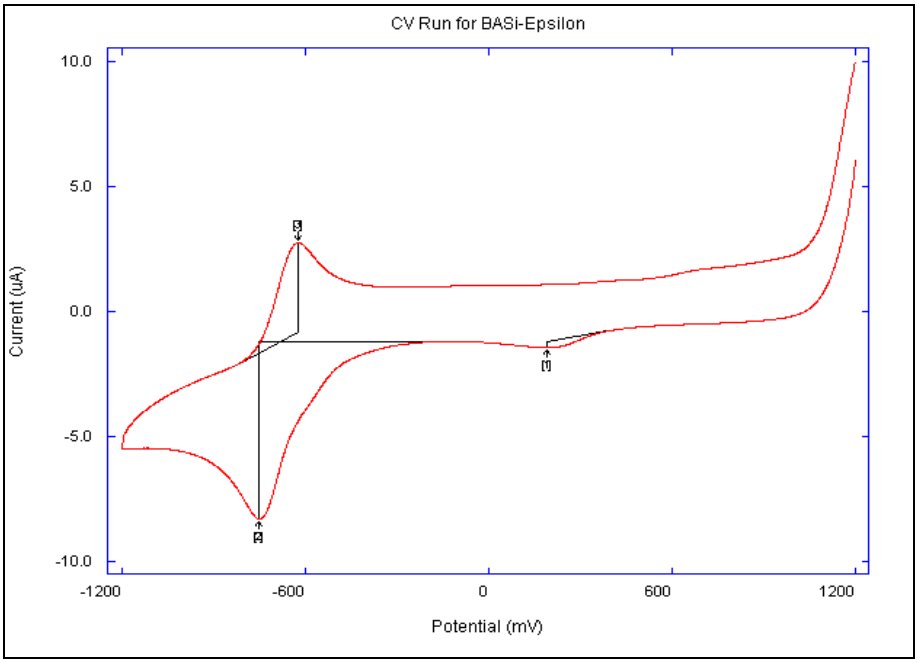


Fig 5: Cyclic voltammogram of {1}.

Table 1: HOMO-LUMO values from electrochemical and electronic spectral data.

Comp.	E_{ox} V (From CV)	E_{HOMO} eV [E_{ox}-$E_{1/2}$+4.8]	Optical band gap from absorption studies (eV) 1242/λ (nm)	E_{LUMO} (E_{HOMO}-optical band gap)	$E_{HOMO-LUMO}$	TD-DFT
{1}	-0.622	3.874	4.740	-0.866	4.740	2.749

3D-Molecular modelling analysis: Because of the lack of explicit crystallographic and morphological information for the studied compounds we carried out computed molecular structures and quantum chemical parameters by using DFT-B3LYP with the 6-311G(d,p) basis set for ligand and the metal complexes LANL2DZ through Gaussian 09 program. The optimized molecular structure of Schiff base ligand HL and their metal complex cis-$[MoO_2(L)_2]${1} are shown in Figures 6 and 7, respectively. The molecular geometry of {1} along with selected six interatomic distances and fifteen bond angles around the metal atom are tabulated in Table 2. The complex geometry is pseudo distorted octahedral geometry with six coordination numbers the four coordination from two O, N-donor HL ligand, the fifth and sixth coordination is bound with two oxo group, and the complex is cis-dioxomolybdenum cis-$[MoO_2)]^{2+}$ species. The above discussion suggested the geometry of the complex is pseudo distorted octahedral. The molecular structure along with the numbering scheme is presented in Figure 7.

Table 2: Selected geometrical parameters of $[MoO_2(L)_2]$ {1}.

Bond Connectivity	(Å)	Bond Connectivity	(°)	Bond Connectivity	(°)
Mo-N(6)	2.221	N(6)-Mo-O(7)	83.982	N(39)-Mo-O(47)	91.672
Mo-O(7)	2.156	N(6)-Mo-N(39)	163.941	N(39)-Mo-O(48)	98.673
Mo-N(39)	2.225	N(6)-Mo-O(40)	83.361	O(40)-Mo-O(47)	88.011
Mo-O(40)	2.150	N(6)-Mo-O(47)	97.759	O(40)-Mo-O(48)	167.390
Mo=O(47)	1.743	N(6)-Mo-O(48)	91.614	O(47)-Mo-O(48)	104.163
Mo=O(48)	1.743	O(7)-Mo-N(39)	84.078		
C(3)-O(7)	1.301	O(7)-Mo-O(40)	79.939		
C(4)=N(6)	1.356	O(7)-Mo-O(47)	167.565		
C(37)=N(39)	1.355	O(7)-Mo-O(48)	88.056		
C(24)=O(40)	1.301	N(39)-Mo-O(40)	84.011		

FMOs and NLO Properties: The molecular orbitals analysis is applied phenomena and it is computer assisted techniques. Herein we carried out the studied compounds, HL and {1}, the iso-surface contour plot of FMOs and their band gap are calculated directly and presented in Figure 8 and the values are summarized in Table 3. For a clear understanding about the FMOs, we use Koopman's theorem [19] for calculation of some quantum chemical parameters. The energy gap ΔE defines the softness and hardness and softness of the molecules. If a molecule has a large energy gap indicate hardness nature and molecule have a small energy gap [20] shows softness nature. There are found very short energy gap of the complex {1} is 2.449 while ligand HL, 4.131 eV, these values are suggested that the stability of complex compound. The NLO properties like dipole moment (μ), polarizability (Δα), anisotropy of the polarizability (Δα) hyperpolarizability *(β)* for the studied compounds are charted in Table 3. The theoretical chemistry provides computed NLO properties of the molecules. Generally, they are highly efficient NLO materials that are mainly consistent with noticeable charge transfer (CT) transitions. The studied compounds are good active NLO materials.

Table 3: Quantum chemical descriptor based on FMOs and NLO properties (μ), (α), (Δα) and *(β)* of the studied compounds.

Parameters	HL	{1}
E_H	-6.340	-6.486
E_L	-2.209	-3.737
ΔE	4.131	2.749
η	-2.066	-1.374
χ	-4.275	-5.111
μ	2.066	1.374
S	-0.242	-3.647
ω	-1.033	-0.687
μ(Dipole moment)	7.104	6.461
α	-242.702×10^{-24}	-312.439×10^{-24}
Δα	26.96×10^{-24}	46.423×10^{-24}
β(0)	168.929×10^{-30}	293.14710^{-30}
Electronic Energy	-1449.724	-2618.413
Spin	Singlet	Singlet

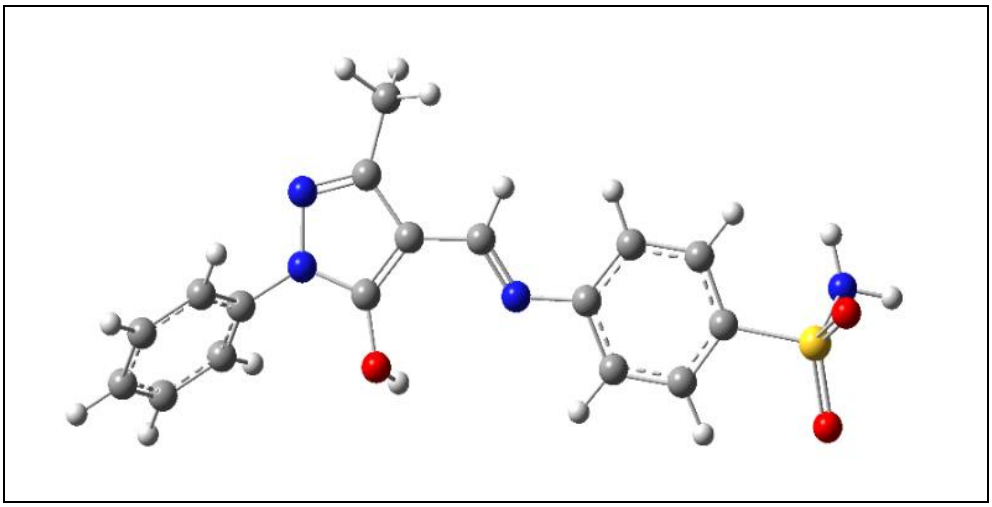


Fig 6: Optimized molecular structure for **HL** with B3LYP and 6-311G(d,p).

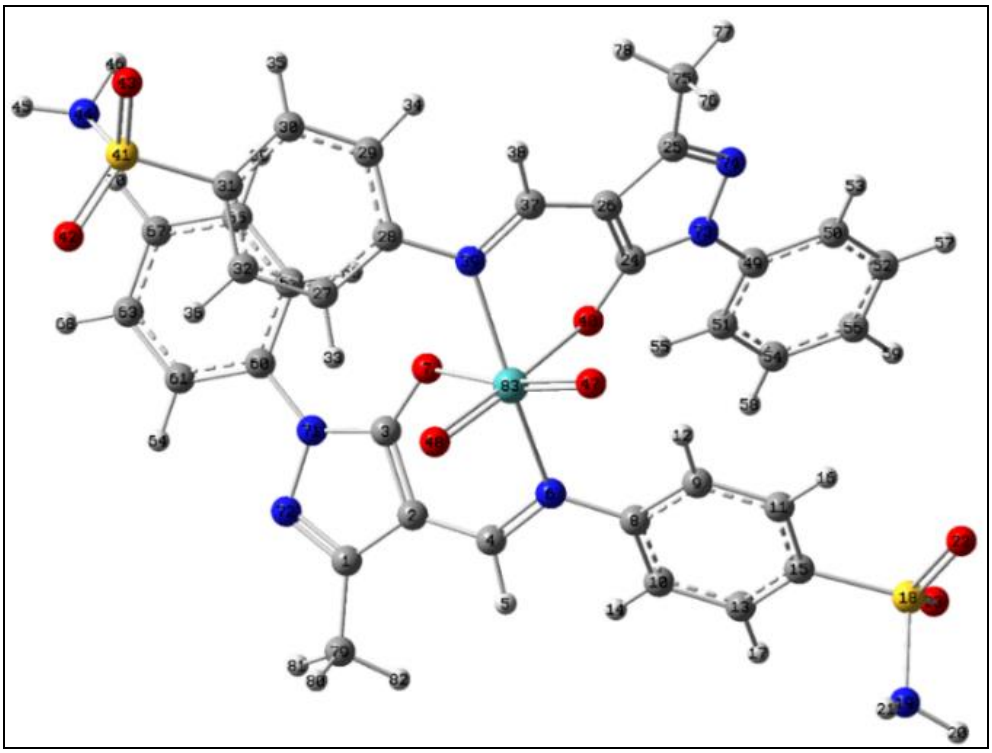


Fig 7: Optimized molecular structure for **{1}** with B3LYP and LANL2DZ.

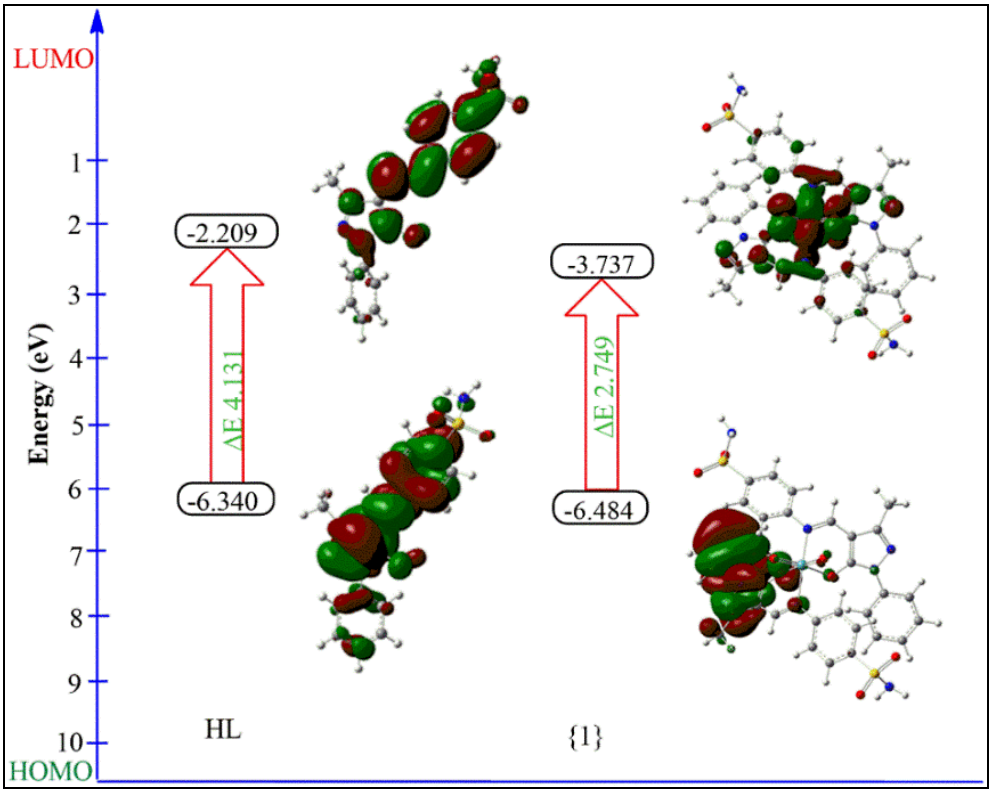


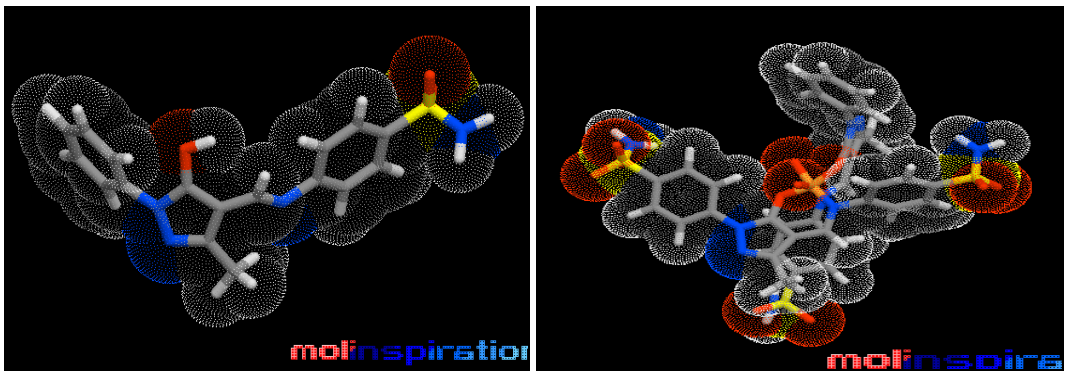
Fig 8: HOMO-LUMO contour plot and energy gap for the studied compounds**.**

Bioactivity score: Pharmaceuticals are characterized by their high potential to interact with a variety of biological targets, which is why they have such an impact on human health. The bioavailability of the studied compounds was predicted using a web-based tool, and the results are listed in Table 4. The bioactivity scores of the compounds are based on various parameters, such as (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), Some research suggests that substances with a score of 0 or higher are highly active while those with a score of 5.0 to 6.9 have moderate activity, and those with a score of 7.0 or above are inactive [21]. The present study's compounds have a value of -0.67 to 0.07, meaning they are predicted to exhibit moderate activity [22]. These molecules are particularly well-suited to serve as drugs because they retain the properties that make them desirable for medicinal purposes, such as demand and addiction potential [23].

Lipinski's rule: The Lipinski's rule is based on the five parameters that's are (RO5) [24]. This is a widely accepted benchmark for drugs development, providing guidance in the description of molecular characteristics that can assist with predicting an orally administered drug's success across various body systems. 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. According to this rule (RO5) a drug for an orally active medication should contain mlogP (≤5), hydrogen bond acceptors (≤10), hydrogen bond donors (≤5), and a molecular weight of (≤500). The orally active medicine in question should typically not exhibit any rule violations. This information is contained within the data table shown in Table 4. The mLogP [25] values for ligand HL (1.94) and complex (-4.69) within the acceptable range, which suggests that these compounds will be able to pass through bio-membranes and exhibit good bioavailability. These molecules qualify as oral therapeutic candidates under RO5 guidelines. 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 [26].

ADMET Prediction: The insilco ADME properties of the studies compounds through web-tool. It is executed to examine whether the studied compounds produce any toxicity after administration in the body or show any pharmacokinetic profile. Keeping for this purpose, the ADMETSAR methodology was used in the current investigation. This studied based on the molecular structure, the desired compounds were characterized for the prediction of their pharmacokinetics properties such as absorption, distribution, metabolism, and elimination (ADME) as well as their pharmacodynamics potential and toxicity behavior, to avoid potential interactions of drugs with anti-targets causing many side effects. Herein, we evaluated various absorption as well as excretion models like (i) aqueous solubility (LogS) (ii) Caco-2 cell permeability, (iii) Blood-Brain Barrier (BBB) penetration, (iv) Human Intestinal Absorption (HIA), and toxicity parameters like (i) carcinogenetic, (ii) LD50 dosage. The ADMET data of ligand HL and their complex {1} are tabulated in Table 4. It is observed that the compounds are having high absorption, and distribution properties indicated by the higher value of

HIA, BBB, and Caco2 permeability, it suggests the more auspicious pharmacokinetic properties. The carcinogenic profile also displayed a non-carcinogenic nature and renal organic cation transporter (ROCT) shows non-inhibitor nature of the studied compounds. One of the important pieces of information collected from ADMETSAR is the computed median lethal dose (LD50) dosage in the rat model (acute rat toxicity) which helps in deciding the lethalness of compounds. Thus, the lower the LD50 value, are more lethal compared to those with higher LD50 values of the compounds. The LD50 values of studied compounds are mostly more than that of the commonly used drug streptomycin (LD50=1.841 mol/kg).



HL {1}

Fig 9: 3D-Molecular structures of ligand studied ligand and their metal complexes obtained through Molinspiration galaxy 3D structure generator v2021.01 beta a

Table 4: Bioactivity score of the synthesized ligand and their metal complex {1}.

Activity	Parameters	HL	{1}
Bioactivity score	GPCR ligand	-0.61	-1.16
	Ion channel modulator	-0.41	-2.18
	Kinase inhibitor	-0.33	-1.72
	Nuclear receptor ligand	-0.93	-2.01
	Protease inhibitor	-0.39	-0.69
	Enzyme inhibitor	-0.20	-1.42
Lipinski's Parameters	% Abs.	70.85	34.96
	TPSA(Å)^2	110.58	214.60
	MlogP	1.94	-4.69
	nOHNH	3	4
	nON	7	16
	nrtb	4	6
	Lipinski's violations	0	2
ADMET activity score	BBB	0.693	0.719
	HIA	0.996	0.936
	Caco2	0.524	0.567
	ROCT	Non-inhibitor	Non-inhibitor
	Carcinogenicity	Non-carcinogens	Non-carcinogens
	LogS	-2.711	-3.348
	LD50 mol/kg	2.024	2.545

Percentage absorption (% abs.) was calculated by % Abs = 109-[0.345 × TPSA], Topological polar surface area (TPSA) (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). Blood-Brain Barrier (BBB), Human Intestinal Absorption (HIA), Caco-2 Permeability (Caco-2) and Renal Organic Cation Transporter (ROCT) (LogS) Aquas solubility

Conclusion

The satisfactory analytical data associated with the computational studies presented above indicate that the complex compound under this investigation is of general composition, *cis*-[$MoO_2(L)_2$]. H_2O [where HL=**(**E)-4-(((5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)methylene)amino)benzene-sulfonamide. The complex so obtained has been characterized based on elemental analyses, infrared and electronic spectral studies. The 3D-molecular modelling and analysis for bond lengths and bond angles have also been carried out for ligand and corresponding complex cis-[$MoO_2(L)_2$].H_2O {1} to substantiate the proposed structure. Based on experimental and computational results revealed that distorted octahedral structure have been proposed for the studied complex. Insilco biological screening indicates that the studied compounds are good drug candidates possessing diverse biological activities.

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