

Research paper

Synthesis, crystal structure, evaluation of urease inhibition potential and the docking studies of cobalt(III) complex based on barbituric acid Schiff base ligand

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ABSTRACT

The discovery of metal-based complexes as potent urease inhibitor is a challenge. In this work, the new $[\text{CoL}_2]\text{NO}_3$ complex of the barbituric acid based ligand, 5-((benzylamino)methylene)-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**HL**) was synthesized. The structural features of the synthesized Co(III) complex were assigned using the single crystal X-ray diffraction techniques, Hirshfeld analysis, DFT calculations and other physicochemical techniques. Its structure comprised CoN_4O_2 coordination sphere with two ligands units (**L**) as mononegative tridentate **NNO**-donor ligand. The potency as urease inhibitor was evaluated *in vitro*. The $[\text{CoL}_2]\text{NO}_3$ complex ($\text{IC}_{50} = 16.0 \pm 0.54 \mu\text{M}$) is better inhibitor than the drug acetohydroxamic acid as a reference ($\text{IC}_{50} = 20.3 \pm 0.43 \mu\text{M}$). The docking studies of the $[\text{CoL}_2]\text{NO}_3$ was carried out using the active center of Jack Bean Urease (PDB 4GY7), and the resulting poses were analyzed visually to understand the interaction pattern.

1. Introduction

Schiff base derivatives form an interesting class of chelating agents for transition metals where large number of studies for chelation with several metals have been reported [1–4]. These compounds have several applications, especially as reagents for the determination of transition metal ions [5,6]. Also these ligands and their metal complexes were reported to possess biological activities, such as antimicrobial, anti-tubercular, anticonvulsant, anti-inflammatory, anti-proliferative activities, antifungal, and α -glucosidase and urease inhibition potential [7–16]. The complexes bearing both organic and inorganic components may possess higher urease inhibitory activities than their precursor's ligands. Recently, a number of metal complexes with urease inhibitory activities have been reported [17–21].

In addition, Schiff bases showed interesting biological activities, [7–16,22]. Among the reported compounds, cobalt complexes have been recommended for urease inhibition. Qin *et al.* have reported some

cobalt complexes based on 4-amino-3,5-bis(pyridin-2-yl)-1,2,4-triazole as a potential agents for urease inhibition [23]. Cui *et al.* [24] reported some cobalt complexes based on Schiff base salicylaldehyde ligand and were tested *in vitro* for jack bean urease inhibition [24].

On the other hand, the privileged structure of barbituric acid which is an important pharmacophore in medicinal chemistry, and was found in many synthetic and natural molecules with broad-spectrum applications, specifically, it has exhibited urease inhibition [25,26], antimicrobial [27,28], anti-inflammatory, and anticancer activities [29].

Therefore, in the present work, a new Co(III) complex; $[\text{CoL}_2]\text{NO}_3$, derived from the 5-((benzylamino)methylene)-1,3-dimethylpyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**HL**) based ligand, was synthesized, and its urease inhibitory activity was evaluated. Additionally, the structure of the $[\text{CoL}_2]\text{NO}_3$ was elucidated by single crystal X-ray diffraction, and density functional theory (DFT) calculations based on quantum theory of atoms in molecules (AIM). The molecular docking study was also performed to reveal the binding interaction of the investigated Co(III)

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complex with the active center of Jack Bean Urease (PDB 4GY7).

2. Experimental

2.1. General methods

Melting points were determined using Mel-Temp apparatus and are uncorrected. Thin Layer Chromatography (TLC) was conducted on silica gel (Kiesel gel G, Merck) and spots were detected under UV light at 254 nm. FT-IR spectra were measured on a Perkin Elmer, Spectrum 100 FT-IR spectrometer (FT-IR, Perkin Elmer, Waltham, MA, USA). ^1H -NMR spectra were recorded with a JEOL spectrometer at 400 MHz. The solvents used were CDCl_3 and $\text{DMSO}-d_6$ for the free ligand **HL** and $[\text{CoL}_2]\text{NO}_3$ Complex, respectively. Chemical shifts (δ) are given in ppm.

2.2. Synthesis of 5-((benzylamino)methylene)-1,3-dimethylpyrimidine-2,4,6-(1H,3H,5H)-trione (**HL**)

A solution of enamine derivative (1 equiv.), with 2-picolylamine (1 equiv.) in MeOH (10 ml) were mixed and stirred at room temperature for 10 mins up 2 h (TLC 20% EtOAc/*n*-hexane). The solvent was evaporated slowly, to provide the corresponding solid product in quantitative yield.

HL obtained as orange powder in yield 99%; m.p: 153 °C; ^1H -NMR (400 MHz, CDCl_3): δ 10.71 (brs, 1H, NH), 8.57 (d, 1H, J = 5.2 Hz, CH =), 8.29 (d, 1H, J = 14.4 Hz, Ar-H₆), 7.67–7.62 (td, 1H, J = 8.0, 1.6 Hz, Ar-H₄), 7.21–7.16 (m, 2H, Ar-H_{3,5}), 4.69 (d, 2H, J = 6.0 Hz, CH₂), 3.26 (s, 6H, 2CH₃); other analytical data are consistent with literature reported by Sing *et al.*, in 2010 [44].

2.3. Synthesis of $[\text{CoL}_2]\text{NO}_3$ complex

$\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (0.18 mmol, 32 mg) dissolved in 10 mL of absolute ethanol was added to absolute ethanolic solution (10 mL) of the ligand **HL** (0.18 mmol, 50 mg) (warm gently to dissolve the ligand). The formed precipitate was filtered then X-ray quality dark violet single crystals of the $[\text{CoL}_2]\text{NO}_3$ complex were obtained in several days upon slow evaporation of the solid product in mixture of EtOH/ H_2O at ambient temperature.

^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.84 (s 1H, N = CH), 8.56 (s 1H, N = CH), 8.39 (d, 1H, J = 14.7 Hz, Pyridine-H), 8.04 (d, 1H, J = 6.2 Hz, Pyridine-H), 7.92–7.85 (m, 2H, Pyridine-H), 7.77 (d, 1H, J = 7.8 Hz, J = 6.0 Hz, CH₂), 6.09 (d, 1H, J = 6.0 Hz, CH₂), 4.82 (d, 2H, J = 6.1 Hz, CH₂), 3.06 and 3.0, Pyridine-H), 7.37 (t, 2H, J = 8.4 Hz, Pyridine-H), 7.26 (t, 1H, J = 6.8 Hz, Pyridine-H), 6.29 (d, 1H, 5 (s, 12H, 4CH₃); IR (KBr) cm^{-1} : 3430, 3150, 3050, 2920, 2860, 2280, 1710, 1670, 1630, 1580, 1384, 1235; LC/MS (ESI): 654.98 $[\text{M}]^+$; Anal. for $\text{C}_{25}\text{H}_{25}\text{CoN}_9\text{O}_9$; Calcd: C, 45.88; H, 3.85; N, 19.26; Found: C, 46.01; H, 3.98; N, 19.43.

2.4. The protocol for urease inhibition assay

Reaction mixtures comprising 25 μL of enzyme (Jack bean urease) solution and 55 μL of buffers containing 100 mM urea were incubated with 5 μL of test compounds (0.5 mM concentration) at 30 °C for 15 min in 96-well plates. Urease activity was determined by measuring ammonia production using the indophenol method as described by weatherburn. Briefly, 45 μL each phenol reagent (1% w/v phenol and 0.005% w/v sodium nitroprusside) and 70 μL of alkali reagent (0.5% w/v NaOH and 0.1% active chloride NaOCl) were added to each well. The increasing absorbance at 630 nm was measured after 50 min, using a microplate reader (Molecular Devices, USA). All reactions were performed in triplicate in a final volume of 200 μL . The results (change in absorbance per min) were processed by using softMax Pro software (Molecular Devices, USA). The entire assays were performed at pH 6.8.

Percentage inhibitions were calculated from the formula $100 - (\text{OD}_{\text{testwell}}/\text{OD}_{\text{control}}) \times 100$. Thiourea was used as the standard inhibitor of urease [30,31].

2.5. Protocol for molecular docking studies

Molecular docking studies were carried out to predict the molecular basis of the observed Urease inhibition demonstrated by the newly synthesized compounds. In this connection, the crystal structure of the Jack Bean Urease under the accession code 4GY7 was retrieved from RCSB-PDB [32]. The protein preparation module in MOE v. 2018.0101 was implemented to fill in the missing loops and atoms, assign bond orders, and for the treatment of formal charges using AMBER 10: EHT force field. The prepared structure was further used to establish the binding mode of the synthesized compounds. The global search coordinates were generated using the centroids of the residues Kcx-490, His-492, His-519, His-545, Asp-633, Ni-901, and Ni-902. The primary placement method was Triangle Matcher, and the London dG was selected as placement scoring method. The Rigid Receptor protocol was used for refinement of the initially generated 30 poses. All the poses were rescored using GBVI/WSA dG re-scoring function. The top-ranked binding pose was analyzed visually using the Protein-Ligand Interaction Profiler (PLIP) web server [33]. The compound was sketched using ChemDraw. The molecule was charged and minimized at neutral pH using the MMFF94x force field [34].

2.6. Crystal structure determination

The crystallographic measurement for the studied $[\text{CoL}_2]\text{NO}_3$ complex was performed using a Bruker D8 Venture equipped with CCD Photon II detector and using monochromated graphite Mo-K α radiation. Absorption corrections were performed by SADABS [35]. Using olex2 [36], the structure of complex **2** was solved, and refined using the ShelXS [37] program package.

2.7. Hirshfeld surface analysis

The topology analyses were performed using Crystal Explorer 17.5 program [38] in order to determine the percentages of the different intermolecular interactions in the crystal structure of the studied $\text{Co}(\text{III})$ complex.

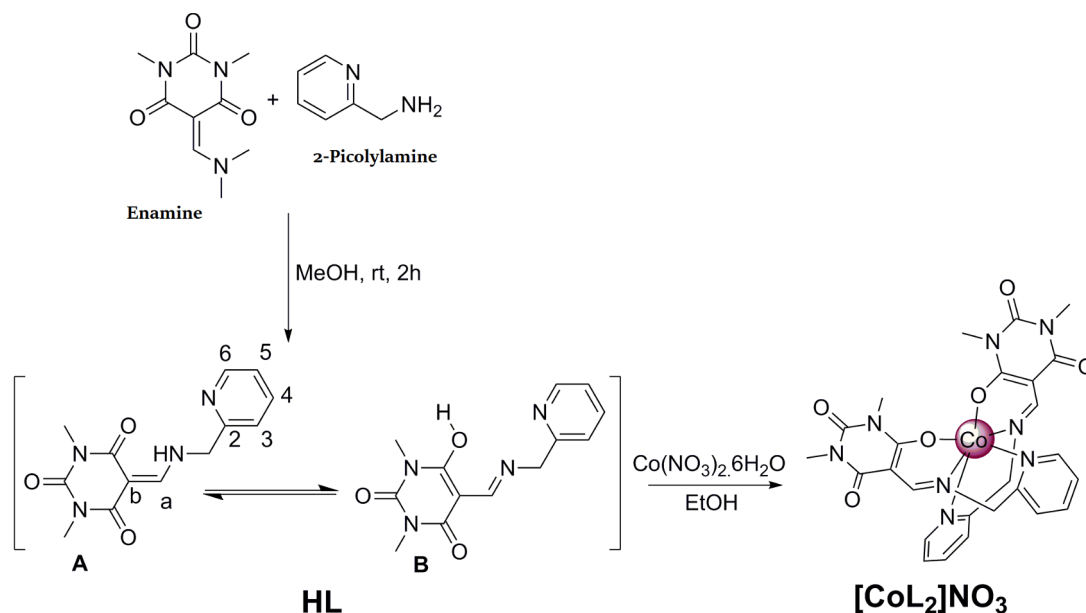
2.8. Computational details

Molecular geometry optimization of the $[\text{CoL}_2]^+$ unit using MPW1PW91 method and TZVP basis sets was performed using Gaussian 09 software [39,40]. In addition, natural bond orbital (NBO) calculations were performed using the Gaussian 09 built in NBO 3.1 [41] program at the optimized and X-ray geometries of the studied complex units. Multiwfn [42] program was used to compute the atoms in molecules (AIM) topological parameters [43] of the Co-N and Co-O interactions at the X-ray geometry.

3. Results and discussion

The 5-((benzylamino)methylene)-1,3-dimethylpyrimidine-2,4,6-(1H,3H,5H)-trione (**HL**) was synthesized by employing new methodology [44]. The reaction proceeds via nucleophilic substitution of the 2-picolylamine with enaminone scaffold in methanolic solution (Scheme 1). The preparation of the metal complex was synthesized via mixing equimolar of the ligand with $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ in absolute ethanol.

The **HL** could exist in two tautomer, enamine with two carbonyl (**HL-A**) or imine with enol form (**HL-B**), the NMR data supported the **HL-A** rather than **HL-B** in solution; [45,46] where it showed a singlet peak at δ 3.26 ppm corresponding to the two *N*-methyl groups, and a



Scheme 1. Synthesis of the ligand (HL) and its $[\text{CoL}_2]\text{NO}_3$ complex.

doublet at δ 4.69 ppm related to the methylene group ($-\text{CH}_2-\text{NH}$). In the **HL-B** form, the two methyl groups have different fields and should appear as two singlets and the methylene group should also appear as a singlet in lower field value in this case. ^{13}C NMR data also supported the structure of **HL-A** rather than **HL-B**. The former showed two peaks at δ 54.8 and 91.4 ppm related to the methylene and the $\text{CH} =$ group ($-\text{CH}_2-\text{NH}-\text{CH}=\text{C}$), respectively, while the peak at δ 164.9 ppm is related to the two carbonyl groups. This data fully supported the enamine structure (**HL-A**) than imine one (**HL-B**), and agreed with the reported data for similar compounds [45,46].

3.1. Urease inhibitory study

The synthesized ligand (HL), and its $[\text{CoL}_2]\text{NO}_3$ complex were evaluated *in vitro* urease enzyme inhibition potential, and compared with those of acetohydroxamic acid as a standard tested compound (Table 1).

From the results shown in Table 1, the cobalt complex $[\text{CoL}_2]\text{NO}_3$ was found to be a potent urease inhibitor with $\text{IC}_{50} = 16.0 \pm 0.54 \mu\text{M}$, and showed more urease inhibition activity than the precursor HL and the tested standard acetohydroxamic acid ($\text{IC}_{50} = 20.3 \pm 0.43 \mu\text{M}$).

3.2. Molecular modeling

The docking studies were carried out by using the crystal structure of Jack Bean Urease (PDB 4GY7), [47] and the resulting poses were analyzed visually to understand the interaction pattern.

The top-ranked docked pose of $[\text{CoL}_2]\text{NO}_3$ is presented in Fig. 1. The coordinated ligand binds in the proximity of Cme592 and His594. The enamine-dione moiety of the coordinated ligand exhibited salt

bridge with the acidic side chain of Asp494. A hydrogen bonding interaction is also observed between Arg439 and the ligand moiety. Moreover, the ligand moiety of the $[\text{CoL}_2]\text{NO}_3$ complex also established hydrophobic contacts with the surrounding residues.

3.3. Crystal structure description

The X-ray diffraction measurement for a single crystal of the studied system showed that the $[\text{CoL}_2]\text{NO}_3$ complex crystallized in the triclinic crystal system and the *P*-1 space group with $Z = 4$, and three formula unit per asymmetric unit (Table 2).

For simplicity, the structure with atom numbering for one of the $[\text{CoL}_2]\text{NO}_3$ complex units is shown in Fig. 2 while the packing of the complex molecular units in the crystal structure is shown in Fig. S6 (Supplementary data). List of bond distances and angles are given in Table 3. The crystal structure of the $[\text{CoL}_2]\text{NO}_3$ complex showed that Co(III) is coordinated with two units of the anionic ligand (**L**). The ligand is coordinated to the Co(III) ion in its enolate form *via* one negatively charged O-atom from the enolate anion with cobalt to oxygen distances ranging from 1.892(3) to 1.915(3) Å for the Co2-O7 and Co3-O13 bonds, respectively. In addition, the ligand coordinating the Co(III) ion *via* two nitrogen atoms; one nitrogen atom from the pyridine moiety and the other one is the azomethine N-atom of the Schiff base moiety. As a general trend, the Co-N(azomethine) distances are slightly shorter than the Co-N(pyridine) coordination interactions. The Co-N distances are in the range of 1.872(6)-1.900(3) Å and 1.911(4)-1.934(4) Å, respectively. Hence the ligand acts as a N_2O^- tridentate chelate. The two Co-N(azomethine) have *trans* configuration with N(azomethine)-Co-N(azomethine) angles (177.20(16)-178.2(2)°) are very close to that for the ideal octahedron (180°). In contrast, the two Co-O and the two Co-N (pyridine), each showed *cis* configuration with O-Co-O and N(pyridine)-Co-N(pyridine) very close to 90°. The O-Co-O and N(pyridine)-Co-N(pyridine) are in the range of 90.67(14)-91.16(13)° and 91.04(15)-92.29(17)°, respectively. As a result, one could conclude that the two planes passing through each ligand in the $[\text{CoL}_2]\text{NO}_3$ complex unit are nearly perpendicular. With two units of this ligand coordinating the Co(III) center, the latter could be considered as *hexa*-coordinated. Based on continuous shape (CShM) measure tool [48–50], the extents of distortion relative to the perfect octahedron are 0.297, 0.299 and 0.260 for Co1, Co2 and Co3, respectively. The corresponding

Table 1
Result of *in vitro* urease enzyme inhibition potential.

Sample Code	Urease inhibitor	
	% Inhibition	$\text{IC}_{50} \pm \text{SEM}(\mu\text{M})$
HL	29.4%	ND
$[\text{CoL}_2]\text{NO}_3$	90.1%	16.0 ± 0.54
STD. Acetohydroxamic acid	94.4%	20.3 ± 0.43

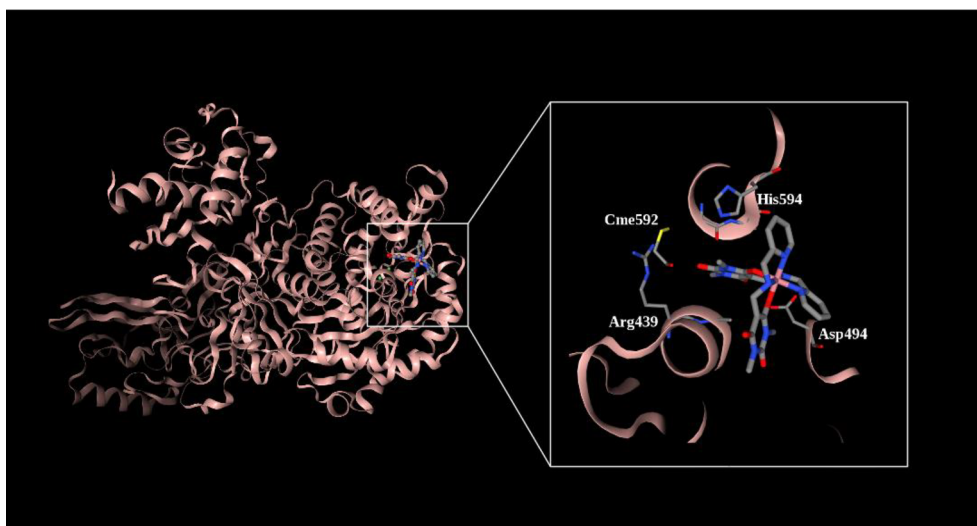


Fig. 1. Simulated binding pose of $[\text{CoL}_2]\text{NO}_3$ with Jack bean urease.

Table 2

Crystal data and structure refinements for the studied Co(III) complex.

CCDC No.	1,967,482	
Empirical formula	$\text{C}_{26}\text{H}_{26}\text{CoN}_9\text{O}_9$	
Formula weight	667.48 g/mol	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P - 1	
Unit cell dimensions	$a = 16.5945(5)$ Å	$\alpha = 92.762(2)^\circ$
	$b = 16.6799(5)$ Å	$\beta = 93.743(2)^\circ$
	$c = 16.8722(5)$ Å	$\gamma = 93.216(2)^\circ$
Volume	$4646.5(2)$ Å ³	
Z	4	
Density (calculated)	1.431 g/cm ³	
Absorption coefficient	4.913 mm ⁻¹	
F(0 0 0)	2064	
Crystal size	$0.03 \times 0.04 \times 0.05$ mm ³	
Theta range for data collection	2.63 to 68.25°	
Index ranges	$-19 \leq h \leq 19$, $-20 \leq k \leq 20$, $-20 \leq l \leq 20$	
Reflections collected	154,617	
Independent reflections	17,001 [R(int) = 0.1223]	
Completeness to theta = 68.25°	99.90%	
Absorption correction	Multiscan	
Max. and min. transmission	0.8670 and 0.7910	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	17,001 / 6 / 1222	
Goodness-of-fit on F ²	1.049	
Final R indices [I > 2sigma(I)]	R1 = 0.0713, wR2 = 0.1676	
R indices (all data)	R1 = 0.1008, wR2 = 0.1832	
Largest diff. peak and hole	1.126 and -0.850	

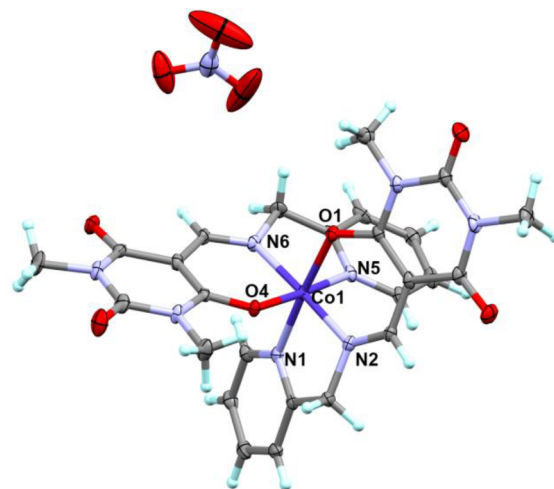


Fig. 2. Crystal structure of one of the $[\text{CoL}_2]\text{NO}_3$ complex units in its crystal structure with atom numbering, showing thermal ellipsoid drawn at 30% probability level.

3.4. Hirshfeld analysis

Analysis of molecular packing of the three $[\text{CoL}_2]^+$ units were analyzed using Hirshfeld topology analysis. All intermolecular contacts and their percentages are listed in Table 4. In addition to the H...H contacts which are common (40.1–40.7%) in all structures, the polar O...H (29.8–30.9%), and nonpolar C...H (15.2–15.6%) contacts are the second most common contacts in the crystal structure of the Co(III) complex. The former appeared as red regions with different intensities indicating that the O...H hydrogen bonding interactions are significantly strong. In contrast, the C...H interactions are generally weak as those appeared as white or blue regions in the d_{norm} surfaces and few of them appeared as very small faded red regions. This fact is further confirmed by the appearance of these interactions as sharper spike for the O...H contacts than the C...H ones in the fingerprint plot of the studied Co-complex (Fig. 3). Interestingly, the d_{norm} surface showed large red regions corresponding to the short C10...O9, C75...O6 and C36...O17 contacts with intermolecular distances of 2.748, 2.770, and 2.780 Å, respectively which are significantly shorter than the sum of the van der Waals radii of the O and C atoms (3.22 Å). Pictorial presentation of the molecular packing via the O...H and C...O interactions is shown in Fig. 4.

values against trigonal prism ideal shape are 15.53, 15.35 and 16.10, respectively. These results confirmed that the coordination configuration around Co(III) centers are very close to the perfect octahedron.

It is worth nothing that DFT calculations using MPW1PW91/TZVP method for the keto **A** and enol **B** (Scheme 1) forms of the ligand HL indicated that the former is less energetic by 33.53 kcal/mol than the latter. It is obvious that the conversion of the keto to enol form in presence of cobalt salt is derived by the extra stability gained from the deprotonation of HL, followed by the chelation of the Co(III) ion to its enolate form which stabilize the complex by chelate effect. This data agreed with the reported data for the copper(II) complex of 1,3-dimethyl-5-acetyl-barbituric acid *o*-hydroxybenzoyl hydrazone ligand [51].

Table 3Bond lengths (Å) and angles (°) for the [CoL₂]NO₃ complex.

Co1-O4	1.893(3)	Co2-O7	1.892(3)	Co3-O13	1.915(3)
Co1-N6	1.899(3)	Co2-N14	1.899(3)	Co3-N18	1.891(4)
Co1-N2	1.900(3)	Co2-N10	1.900(3)	Co3-N22	1.872(6)
Co1-O1	1.904(3)	Co2-O10	1.909(3)	Co3-O16	1.893(3)
Co1-N1	1.911(4)	Co2-N9	1.914(4)	Co3-N17	1.919(4)
Co1-N5	1.931(4)	Co2-N13	1.934(4)	Co3-N21	1.928(5)
O4-Co1-N6	93.12(14)	O7-Co2-N14	93.03(14)	N22-Co3-O16	93.3(2)
O4-Co1-N2	84.99(14)	O7-Co2-N10	84.67(14)	N18-Co3-O16	85.26(15)
N6-Co1-N2	177.53(16)	N14-Co2-N10	177.20(16)	N22-Co3-N18	178.2(2)
O4-Co1-O1	90.76(13)	O7-Co2-O10	91.16(13)	N22-Co3-O13	88.24(17)
N6-Co1-O1	88.70(14)	N14-Co2-O10	89.05(14)	N18-Co3-O13	92.82(16)
N2-Co1-O1	92.92(14)	N10-Co2-O10	92.57(14)	O16-Co3-O13	90.67(14)
O4-Co1-N1	89.94(14)	O7-Co2-N9	89.96(15)	N22-Co3-N17	94.93(19)
N6-Co1-N1	94.78(15)	N14-Co2-N9	94.36(16)	N18-Co3-N17	84.01(18)
N2-Co1-N1	83.63(15)	N10-Co2-N9	84.07(16)	O16-Co3-N17	88.68(15)
O1-Co1-N1	176.41(14)	O10-Co2-N9	176.35(14)	O13-Co3-N17	176.80(17)
O4-Co1-N5	177.22(15)	O7-Co2-N13	177.11(15)	N22-Co3-N21	84.8(3)
N6-Co1-N5	84.21(16)	N14-Co2-N13	84.43(16)	N18-Co3-N21	96.6(2)
N2-Co1-N5	97.70(15)	N10-Co2-N13	97.91(16)	O16-Co3-N21	178.0(2)
O1-Co1-N5	88.42(14)	O10-Co2-N13	87.42(14)	O13-Co3-N21	88.46(16)
N1-Co1-N5	91.04(15)	N9-Co2-N13	91.61(16)	N17-Co3-N21	92.29(17)

Table 4

The intermolecular contacts and their percentages for the three cobalt (III) complex units.

Contact	Co1	Co2	Co3
H...H	40.3	40.1	40.7
C...O	4.4	4.5	4.3
O...H	30.9	30.6	29.8
C...H	15.2	15.3	15.6
C...N	1.9	1.8	2.0
N...H	2.9	3.1	2.9
C...C	1.9	1.8	1.8
O...O	1.1	1.1	1.3
N...O	1.4	1.7	1.6

3.5. AIM topology analysis

The present section aims to shed the light on the nature and strength of the Co-O and Co-N bonds in the new Co(III) complex [52–58]. List of the calculated topological parameters are given in Table 5. The electron density ($\rho(r)$) values of the Co-O and Co-N coordinate bonds are in the range of 0.0452–0.0790 and 0.0875–0.0975 a.u., respectively. The $\rho(r)$ values are significantly lower than 0.1 a.u. for all Co-O bonds. On other hand, the corresponding values for the Co-N bonds are close to 0.1 a.u. Based on these results, the majority of the Co-O interactions are considered weak and mainly belong to closed shell interactions while the Co-N coordinate bonds are relatively strong and have the characteristics of covalent bond characters. In agreement with this results, the Co-O bonds have positive total energy density ($H(r)$) and $V(r)/G(r) < 1$

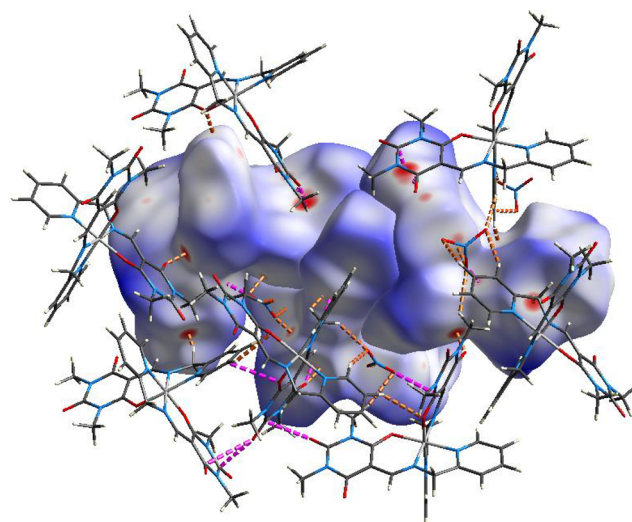


Fig. 4. The O...H (orange dotted line) and C...O (pink dotted line) strong contacts among the complex molecular units based on Hirshfeld analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

which are the typical characteristics of the closed shell interactions. The only exceptions from this conclusion are the Co2-O10 and Co3-O13 bonds. In contrast, the Co-N bonds have the opposite of these criteria (negative $H(r)$ and $V(r)/G(r) > 1$) indicating some covalent

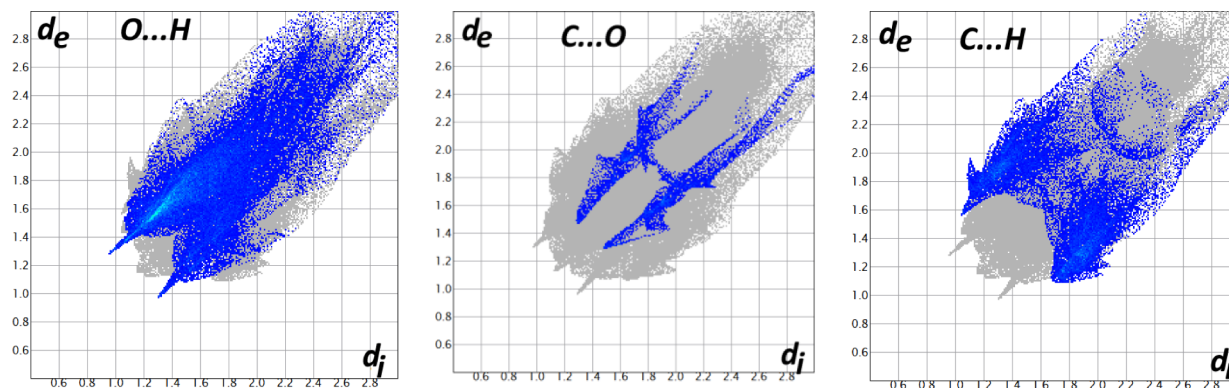


Fig. 3. The fingerprint plots of the O...H, C...O and C...H contacts.

Table 5
AIM Topological parameters (a.u.) of the Co-O and Co-N coordinate bonds.

Bond	P(r)	G(r)	V(r)	E _{int} ^a	H(r)	V(r)/G(r)
Co1-O1	0.0448	0.1409	-0.1342	42.11	0.0067	0.9523
Co1-N2	0.0920	0.1861	-0.1987	62.34	-0.0126	1.0677
Co1-N1	0.0975	0.1785	-0.1989	62.40	-0.0204	1.1145
Co1-O4	0.0452	0.1490	-0.1400	43.92	0.0090	0.9394
Co1-N5	0.0938	0.1661	-0.1863	58.46	-0.0202	1.1215
Co1-N6	0.0908	0.1948	-0.2038	63.94	-0.0090	1.0461
Co2-O7	0.0447	0.1508	-0.1413	44.33	0.0095	0.9371
Co2-N14	0.0897	0.1920	-0.2018	63.30	-0.0098	1.0511
Co2-N13	0.0923	0.1655	-0.1860	58.37	-0.0206	1.1242
Co2-O10	0.0790	0.1548	-0.1678	52.66	-0.0130	1.0843
Co2-N9	0.0884	0.1750	-0.1906	59.80	-0.0156	1.0891
Co2-N10	0.0907	0.1840	-0.1969	61.77	-0.0128	1.0697
Co3-O13	0.0778	0.1539	-0.1659	52.06	-0.0121	1.0784
Co3-N18	0.0919	0.1916	-0.2033	63.78	-0.0117	1.0608
Co3-N17	0.0875	0.1718	-0.1875	58.82	-0.0157	1.0914
Co3-O16	0.0455	0.1445	-0.1369	42.96	0.0075	0.9477
Co3-N22	0.0945	0.2095	-0.2177	68.29	-0.0082	1.0390
Co3-N21	0.0925	0.1694	-0.1891	59.34	-0.0197	1.1161

^a kcal/mol

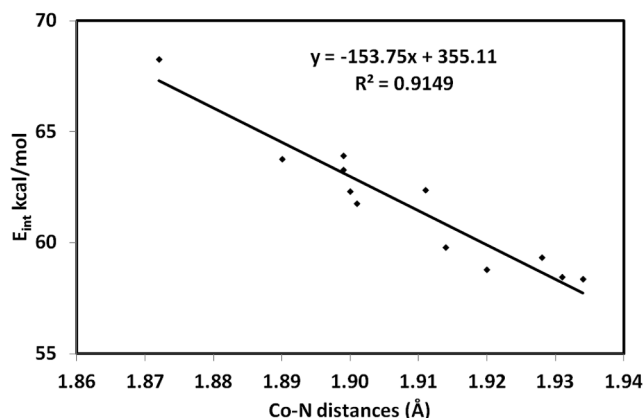


Fig. 5. Correlation between the Co-N distances and interactions energies using Espinosa relation [58].

characteristics for these bonds. The interaction energies (E_{int}) [59] of the Co-O and Co-N coordination interactions are given in the same table. It is clear that, the Co2-O10 (52.66 kcal/mol) and Co3-O13 (52.06 kcal/mol) bonds have the highest interaction energies among the rest of the Co-O bonds. On other hand, the Co-N bonds showed good correlations between the Espinosa interaction energies (E_{int}) and the corresponding bond distances with correlation coefficients of $R^2 = 0.914$ (Fig. 5). In chemical sense, shorter bonds are stronger and hence have higher interaction energies.

3.6. Natural population analysis

For the $[\text{CoL}_2]^+$ unit, the natural charges of the Co1, Co2 and Co3 atomic sites at the X-ray geometry are calculated to be 0.359, 0.362 and 0.349 e, respectively. The corresponding value at the optimized geometry of the studied complex unit is calculated to be 0.405 e. The results indicated that the two anionic tridentate ligand units transferred significant amount of electron density to the Co(III) ion, as a result its charge density is reduced up to 2.651 e. The organic ligand negative charge density are significantly shifted to higher positive charge of 0.320, 0.319 and 0.325 e for the coordinated L^- in the Co1, Co2 and Co3 complex units, respectively. The corresponding value is calculated to be 0.298 e at the optimized geometry. Here we considered the average net charge densities of the two coordinated ligand units. In this regard, the amounts of electron density transferred from each ligand are 1.320, 1.319, 1.325 and 1.298 e, respectively.

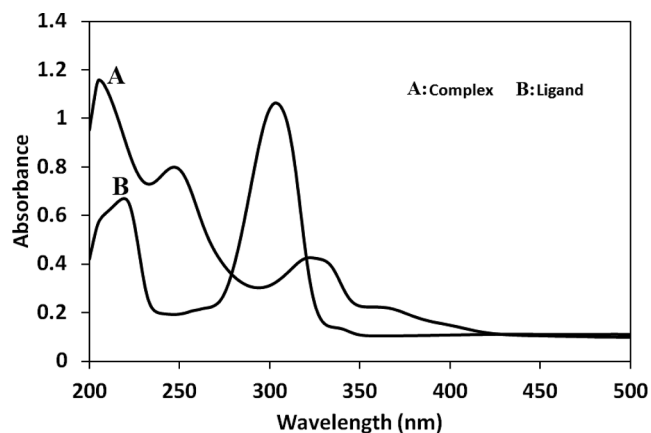


Fig. 6. The electronic spectra of the studied ligand and its Co(III) complex.

3.7. Electronic spectra

The UV-VIS spectra of **HL**, and the $[\text{CoL}_2]\text{NO}_3$ complex were recorded in ethanol in the range 200–800 nm at room temperature (Fig. 6). In the electronic spectrum of **HL**, three intense peaks were observed at 207(Sh), 216, and 301 nm. The two intense absorption bands in the high energy region of 207–216 nm indicates $\pi-\pi^*$ transitions. In the Co(III) complex, the band and shoulder were merged in one band at higher energy of 205 nm. The two longer wavelength bands observed at 323 and 357 nm in the complex could be assigned to the $^1\text{A}_{1g} \rightarrow ^1\text{T}_{1g}$ and $^1\text{A}_{1g} \rightarrow ^1\text{T}_{2g}$ [60,61] transitions, respectively which confirm the low spin state of the studied Co(III) complex. The high intensity band observed at 301 nm in the spectra of **HL** are lowered in intensity and shifted to the high energy region, in agreement with the assignment of this band as $n-\pi^*$ transition.

4. Conclusions

In conclusion we report here the synthesis, characterization and single crystal X-ray structure of a new $[\text{CoL}_2]\text{NO}_3$ complex. Its structure comprised of hexa-coordinated Co(III) ion with the barbiturate based ligand as mononegative N_2O^- tridentate chelate. The X-ray data showed the complex in the imine-enolate structure rather than the enamine-dione structure. The new $[\text{CoL}_2]\text{NO}_3$ complex showed a potent urease inhibitory activities, with IC_{50} value of $(16.0 \pm 0.54 \mu\text{M})$. Molecular docking study of the complex with the Jack bean urease indicated that the Co(III) complex of the barbituric acid based ligand (**HL**) fits well with active pocket of the urease. The $[\text{CoL}_2]\text{NO}_3$ complex may be used as precursors for the design of novel urease inhibitors.

CCRediT authorship contribution statement

Assem Barakat: Conceptualization, Supervision, Data curation, Writing - review & editing. **Saied M. Soliman:** Software, Validation, Writing - review & editing. **M. Ali:** Investigation, Methodology, Writing - review & editing. **Adel Elmarghany:** Investigation, Methodology, Writing - review & editing. **Abdullah Mohammed Al-Majid:** Visualization, Validation, Writing - review & editing. **Sammer Yousuf:** Software, Validation, Writing - review & editing. **Zaheer Ul-Haq:** Software, Validation, Writing - review & editing. **M. Iqbal Choudhary:** Visualization, Validation, Writing - review & editing. **Ayman El-Faham:** Visualization, Validation, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ica.2019.119405>.

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