

# Synthesis and crystal structure studies of a new complex of Co(III)-Schiff base derivative derived from isonicotinohydrazide

## ABSTRACT

A new Co(III) complex prepared by the reaction of *N*-(1-(pyridin-2 yl)ethylidene)isonicotinohydrazide (H<sub>2</sub>L) with Co(II) ion is reported in this paper. The H<sub>2</sub>L ligand is structurally characterized by elemental analysis, NMR, and infrared spectroscopies. The mononuclear complex [Co(HL)<sub>2</sub>].Cl·3H<sub>2</sub>O (1), is characterized by infrared spectroscopy, elemental analysis, conductance, magnetic room temperature measurement and single X-ray diffraction. The complex crystallizes in the monoclinic system with space group P21/c. The parameters of the unit cell are a = 9.6818(3) Å; b = 25.1587(6) Å; c = 11.5481(3) Å; β = 101.797(3) °; Z = 4; R<sub>int</sub> = 0.0313 and wR(F<sub>2</sub>) = 0.0812. The asymmetric unit of the compound contains a discrete [Co(HL)<sub>2</sub>]<sup>+</sup> cation one free chloride anion and three uncoordinated water molecules. In the discrete cation one Co<sup>3+</sup> ion two organic ligand molecules are present. The coordination polyhedron around the Co<sup>3+</sup> center is best described as a distorted octahedral with CoN<sub>4</sub>O<sub>2</sub> chromophore. The crystal structure of the complex is stabilized by intramolecular and intermolecular hydrogen bonds.

**Keywords:** Schiff base; isonicotinohydrazide; cobalt; X-ray diffraction; complex; mononuclear

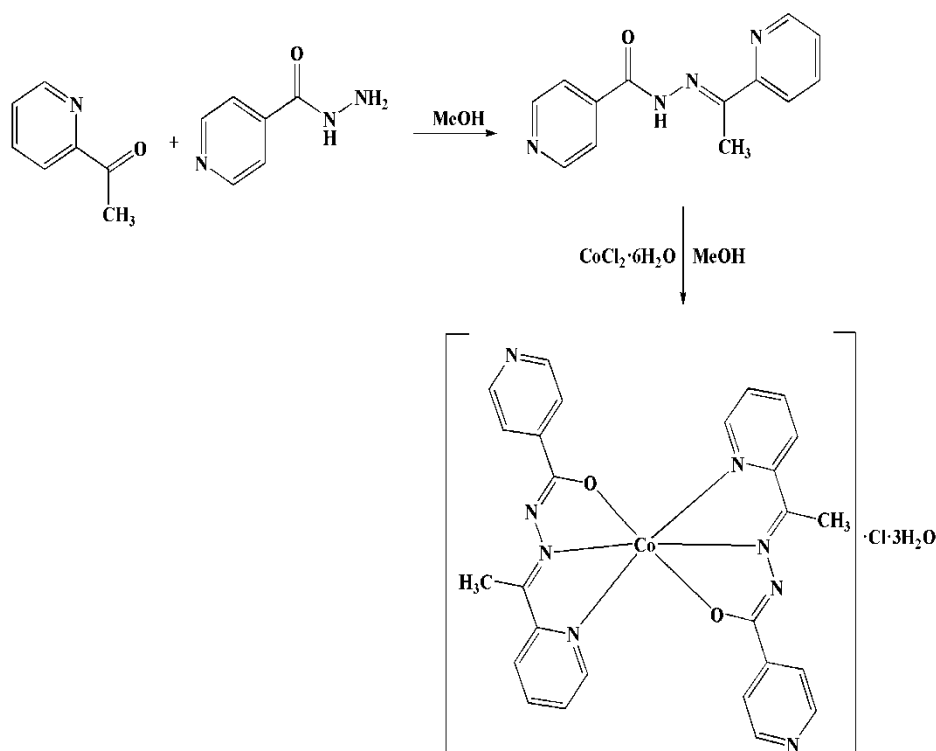
## 1. INTRODUCTION

In recent years, the chemical properties and biological activity of acylhydrazones have attracted much attention from chemists [1,2]. Acylhydrazones, due to their azometine moieties –C=N–NH–CO–, are good intermediates in the synthesis of various heterocyclic compounds [3-8] and they are also effective organic compounds in their own right due to their biological activities [9] and their chemical and industrial versatility [10–13]. “Acylhydrazones are easily synthesized and can be obtained by a condensation reaction of an aldehyde or a ketone with a derivative of the hydrazide class in the presence of an alcoholic solvent, generally at reflux, and in an acidic medium [14–19] or in neutral medium” [20-22]. “They can appear structurally in the form of four isomers, two of which are geometric isomers (E/Z) and are due to the C=N double bond, and two are conformers (syn/anti) and are due to the N-N bond” [7,23]. Acylhydrazones have significant importance in the pharmaceutical field thanks to their numerous biological properties with multiple therapeutic indications. In recent studies performed with these derivatives, the following properties have been reported: antitumor [24-29], cytotoxic [30], antibacterial [6,31-34], antifungal [35,36], antiviral [37,38], antiparasitic [39-41], anti-inflammatory [42-44], analgesic [45-47], enzyme inhibition [48-49], antioxidant [50-52], antidiabetic [53], and anticonvulsant [54]. In coordination chemistry, acylhydrazones derived from isonicotinohydrazine have been widely used as Schiff bases to synthesize stable complexes with transition metal or lanthanide ions [55-57]. In this paper, we report the synthesis, spectroscopic characterization, and crystal structure of a new complex [Co(HL)<sub>2</sub>].Cl·3H<sub>2</sub>O derived from a Schiff base (H<sub>2</sub>L) obtained from a condensation reaction between isonicotinohydrazide and acetylpyridine in the presence of acetic acid.

## 2. Materials and Methods

### 2.1. Starting materials and instrumentations

“Commercially available 2-acetylpyridine, isonicotinohydrazine and cobalt chloride salt were purchased from Aldrich and used without further purification. The solvents were reagent grade and were purified by usual methods. Elemental analyses were carried out using a VxRio EL Instrument. The IR spectra were recorded on a FTIR Perkin-Elmer UV/Visible spectrophotometer Lambda 365 (1000–200 nm). The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the Schiff bases were recorded in DMSO-d<sub>6</sub> on a BRUKER 500 MHz spectrometer at room temperature using TMS as an internal reference. The molar conductance of 10<sup>-3</sup> M solutions of the metal complexes in DMF was measured at 25 °C using a WTW LF-330 conductivity meter with a WTW conductivity cell” [3]. Room temperature magnetic susceptibilities of the powdered samples were measured using a Johnson Matthey scientific magnetic susceptibility balance (Calibrant: Hg[Co(SCN)<sub>4</sub>]).



**Scheme 1. Synthetic pathway of the ligand and the complex**

## 2.2. Synthesis of the ligand H<sub>2</sub>L

In a round bottomed flask containing 20 mL of methanol, 2 g (14.58 mmol) of isonicotinic acid hydrazide were introduced and stirred until completely dissolved. Thus 1.668 mL (14.58 mmol) of 2-acetylpyridine and a few drops of acetic acid were added, and an orange color was developed. The reaction mixture was refluxed for 4 hours to obtain a brown precipitate which was recovered by filtration and washing with 2 x 10 mL of methanol. M.P. 154°C. Yield 74%. Anal. calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>O: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.96; H, 5.01; N, 23.30 %. FT-IR (ATR,  $\nu$ , cm<sup>-1</sup>): 3182, 1667, 1622, 1581, 1563, 1550, 1495, 1455, 1428, 1217, 1150, 990, 622. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ , ppm): 2.49 (s, 3H, -CH<sub>3</sub>); 7.40–8.93 (m, 8H, H<sub>Py</sub>); 11.23 (s, 1H, HN-C=O). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>,  $\delta$ , ppm) 163.35 (C=O); 156.77 (C<sub>ipso,Py</sub>); 155.35 (C=N); 151.33 (C<sub>Py</sub>); 149.98 (C<sub>Py</sub>); 141.47 (C<sub>ipso,Py</sub>); 137.12 (C<sub>Py</sub>); 124.85 (C<sub>Py</sub>); 122.42 (C<sub>Py</sub>); 121.02 (C<sub>Py</sub>). 13.37 (-CH<sub>3</sub>).

## 2.3. Synthesis of the complex [Co(HL)<sub>2</sub>]-Cl·3H<sub>2</sub>O

To methanolic solution (10 mL) of the ligand H<sub>2</sub>L, 0.2 g (0.832 mmol) a solution of the CoCl<sub>2</sub>·6H<sub>2</sub>O salt 0.989 g (0.416 mmol) in methanol (10 mL) was added. The solution was stirred under reflux for two hours. The dark red solution obtained was filtered and left to slow evaporation. After one week, dark red crystals suitable for X-ray analysis were collected. M.p. : 240 °C. Yield: 70.42%. Anal. Calc for C<sub>26</sub>H<sub>28</sub>N<sub>8</sub>O<sub>5</sub>ClCo: C, 49.81, H, 4.50, N, 17.87, Cl, 5.56. Found: C, 49.79; H, 4.47; N, 17.90; Cl, 5.58. IR (cm<sup>-1</sup>): 3400 (OH), 3180 (NH), 1615 (O-C=N)<sub>iminol</sub>, 1603 (C=N)<sub>imine</sub>, 1567 (C<sub>Ar</sub>=N), 1548-1438 (C<sub>Ar</sub>=C<sub>Ar</sub>); 1313 (O-C)<sub>enol</sub>; 1054 (N-N); 824  $\delta$ (H<sub>2</sub>O). Diamagnetic. UV-vis (solution, DMF,  $\lambda$  (nm)): 215-255; 302; 438.  $\Lambda$  (Ω<sup>-1</sup>·cm<sup>2</sup>·mol<sup>-1</sup>): 69.15 (fresh solution) and 70.51 (two weeks after).

## 2.4. Crystal structure determination

“Crystals suitable for X-diffraction, of the reported compound, were grown by slow evaporation of MeOH solution of the complex. Details of the X-rays crystal structure solution and refinement are given in Table 1. Diffraction data were collected using a Rigaku Oxford diffractometer with graphite monochromatized Mo K $\alpha$  radiation ( $\lambda$  = 0.71073 Å). All data were corrected for Lorentz and polarization effects. No absorption correction was applied. Using Olex2 the structures were solved by intrinsic phasing methods with SHELXT and SHELXL was used for full matrix least squares refinement”. [58-60] “The hydrogen atoms of water molecules and NH groups were located in the Fourier difference maps and refined. Others H atoms were geometrically optimized and refined as riding model by AFIX instructions. Molecular graphics were generated using ORTEP-3” [61].

**Table 1. Crystal data and structure refinement for [Co(HL)<sub>2</sub>]-Cl·3H<sub>2</sub>O**

Empirical formula	C <sub>26</sub> H <sub>28</sub> ClCoN <sub>8</sub> O <sub>5</sub>
Formula weight	626.94
Temperature (K)	175.00(10)
Radiation MoK $\alpha$ ( $\lambda$ )	0.7107(3)
Crystal system	Monoclinic
Space group	P2 <sub>1</sub> /c
a ( $\text{\AA}$ )	9.6818(3)
b ( $\text{\AA}$ )	25.1587(6)
c ( $\text{\AA}$ )	11.5481(3)
$\alpha$ ( $^\circ$ )	90
$\beta$ ( $^\circ$ )	101.797(3)
$\gamma$ ( $^\circ$ )	90
Volume ( $\text{\AA}^3$ )	2753.49(13)
Z	4
$\rho_{\text{calc}}$ ( $\text{g}/\text{cm}^3$ )	1.512
$\mu$ ( $\text{mm}^{-1}$ )	0.773
F(000)	1296.0
Crystal size ( $\text{mm}^3$ )	0.24 $\times$ 0.06 $\times$ 0.03
2 $\theta$ range for data collection/ $^\circ$	4.298 to 57.398
Index ranges	-12 $\leq$ h $\leq$ 13, -27 $\leq$ k $\leq$ 33, -15 $\leq$ l $\leq$ 15
Reflections collected	44070
Independent reflections	7110 [ $R_{\text{int}} = 0.0313$ , $R_{\text{sigma}} = 0.0253$ ]
Data/restraints/parameters	7109/0/381
Goodness-of-fit on $F^2$	1.060
Final R indexes [ $I \geq 2\sigma(I)$ ]	$R_1 = 0.0309$ , $wR_2 = 0.0779$
Final R indexes [all data]	$R_1 = 0.0383$ , $wR_2 = 0.0812$

### 3. Results and Discussion

#### 3.1. General study

The synthesis of the Schiff base H<sub>2</sub>L is achieved in a one-step procedure using the direct condensation of isonicotohydrazine and 2-acetylpyridine in 1/1 ratio. The coordination abilities of the H<sub>2</sub>L with cobalt (II) chloride salt was investigated in 2:1 ligand/metal ratio in methanol solutions (Scheme 1). The Co(III) complex prepared at reflux gave a solution which after evaporation gave single crystals. The crystal structure of the complex is confirmed by X-ray diffraction. The complex is characterized by elemental analysis, infrared and UV-visible spectroscopies, and molar conductivity. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the ligand N'-(1-(pyridin-2-yl)ethylidene)isonicotinohydrazide (H<sub>2</sub>L) are recorded in DMSO-d<sub>6</sub> as shown in the experimental section. The <sup>1</sup>H NMR spectrum shows a complex signal in the range 8.13-7.40 ppm integrating a total of 9 protons attributed to the protons of the two pyridine rings. The singlet signal at 2.49 ppm representing 3 protons is assigned to the methyl group. The broad signal centered at 11.23 ppm is due to a -OH group which reveals the iminolisation of the ligand in DMSO. The <sup>13</sup>C NMR spectrum shows the presence of a signal at 153 ppm attributed to the carbon atom carrying the iminol function. The solid state IR spectrum of the ligand reveals bands at 3182 cm<sup>-1</sup>, 1677 cm<sup>-1</sup>, 1622 cm<sup>-1</sup> and 1582 cm<sup>-1</sup> which are respectively assigned to  $\nu_{\text{(NH)}}$ ,  $\nu_{\text{(C=O)}}$ ,  $\nu_{\text{(C=N)imine}}$  and  $\nu_{\text{(C=Ar=N)}}$  [62, 63] indicating the non-iminolisation of the ligand in its solid form. Upon reaction of the ligand and cobalt (II) chloride the spectrum of the resulting complex shows a shift of the bands  $\nu_{\text{(C=N)imine}}$  and  $\nu_{\text{(C=Ar=N)}}$  towards low frequencies and the disappearance of the  $\nu_{\text{(C=O)}}$ . The  $\nu_{\text{(C=N)imine}}$  and  $\nu_{\text{(C=Ar=N)}}$  appear, respectively, at 1603 cm<sup>-1</sup> and 1567 cm<sup>-1</sup> on the spectrum of the complex. This is indicative of the involvement of the nitrogen atoms of the imine function and pyridine ring in the coordination of the metal ion. The absence of the  $\nu_{\text{(NH)}}$ ,  $\nu_{\text{(C=O)}}$  and  $\nu_{\text{(OH)enol}}$  vibration bands and the appearance of the  $\nu_{\text{(C-O)enol}}$  band at 1313 cm<sup>-1</sup> show that iminolisation of the ligand undergoes during complexation and that the atom of oxygen enol participates in the coordination of the metal ion. The broad band which appears at 3400 cm<sup>-1</sup> on the spectrum of the complex is due to the presence of uncoordinated water molecules. The molar conductivity measurements of the complex taken from a fresh solution of DMF and after fifteen days of storage [69.15  $\Omega^{-1}\cdot\text{cm}^2\cdot\text{mol}^{-1}$  and 70.51  $\Omega^{-1}\cdot\text{cm}^2\cdot\text{mol}^{-1}$ ] indicate that the complex is 1:1 electrolyte type according to Geary [64]. "The small variation in the values obtained shows that the complex is stable

in the DMF solution. The electronic spectrum of the complex shows three broad bands at 215 nm, 302 nm and 438 nm. The bands at 215 nm and 302 nm are due to the intraligand transitions  $\pi \rightarrow \pi^*$  and  $n \rightarrow \pi^*$ , respectively. The band centered at 438 nm is attributed to LMCT [65]. "Room temperature magnetic susceptibility measurement shows that the complex **1** is diamagnetic as expected for low-spin cobalt (III) complexes" [66].

### 3.2. Description of the crystal structure of the complex [Co(HL)<sub>2</sub>·Cl·3H<sub>2</sub>O (**1**)

The complex crystallizes in the monoclinic system with the space group of  $P2_1/c$ . The crystallographic data and refinement of the complex are recorded in the Table 1. The selected bond distances and angles are listed in Table 2, and the ORTEP representation of the structure is illustrated in Fig. 2. The asymmetric unit of the complex contains a discrete [Co(HL)<sub>2</sub>]<sup>+</sup> cation, three uncoordinated water molecules and one chloride ion ensuring the neutrality of the complex. In the discrete cation, one Co(III) ion and two molecules of the ligand are present. Each ligand molecule acts in its monodeprotonated iminol form in tridentate fashion. It coordinates the ion Co(III) through one enol oxygen atom, one azomethine nitrogen atom, and one pyridine ring nitrogen atom, yielding a hexacoordinated metal ion. The coordination geometry around the Co(III) cation is best described as a distorted octahedral geometry. The two enolic oxygen atoms [O1, O2] and the two pyridine nitrogen atoms [N1, N5] form the basal plane (rms 0.2410) with Co1 0.054 (4) Å out of this plane. The apical positions are occupied by two azomethine nitrogen atoms. The cisoid angles values in the basal plane deviated from the ideal value of 90° [O1–Co1–O2 = 90.39 (4) ; O1–Co1–N5 = 92.86 (5); N1–Co1–N5 = 90.21 (5) ; N1–Co1–O2 = 91.02 (5)] with a sum of 364.48°. The angle subtended by the atoms in apical positions (N2–Co1–N6 = 179.12(5)°) is slightly different of the ideal value of 180°. Each ligand forms two five membered rings of type CoNCCCN and CoOCNN upon coordination. The bites angles subtended by the atom of the five membered rings coordinated to the Co ion are in the range [81.72(5)°–82.17 (5)°]. The ligand molecules are quite planar [rms 0.1170 and 0.0875] with O1 out of plane of 0.1170 Å for one ligand and C16 0.0875 Å out of plane for the second ligand. In the complex the two coordinated ligand molecules are quite perpendicular and form a dihedral angle of 86.12 (1)°. These observations indicate the slight distortion of the octahedral polyhedron. The distances Co–N<sub>pyridine</sub> and Co–N<sub>imine</sub> falls in the range [1.9413 (12) Å–1.9231 (12) Å] and [1.8584 Å–1.8605 (11) Å], respectively, and agree with the values reported for similar compounds [67]. The distances O–C [Co1–O1 = 1.9164 (10) Å and Co1–O2 = 1.9390 (10) Å] are characteristic of a single bond confirming the enol form of the ligand in the complex. The crystal packing of the compound is stabilized by unclassical intramolecular and intermolecular hydrogen bonds C14–H14...N2 and C1–H1...N6 and intermolecular, C1–H1...O3<sup>i</sup> (i = x–1, –y+3/2, z–1/2), C23–H23...O2<sup>ii</sup> (ii = x, –y+3/2, z–1/2), C15–H15...Cl1<sup>iii</sup> (iii = –x+2, y+1/2, –z+3/2), C4–H4...O4<sup>iv</sup> (iv = x–1, –y+3/2, z+1/2), C17–H17...O5<sup>v</sup> (v = –x+2, y+1/2, –z+1/2), C12–H12...Cl1<sup>vi</sup> (vi = –x+2, –y+1, –z+1), C25–H25...Cl1<sup>vii</sup> (vii = –x+1, –y+1, –z+1)]. These hydrogen bonds connect the units forming a two-dimensional planar structure in the *ab* plane (Figure 1, Table 3).

**Table 2 . Selected bond distances [Å] and angles [°] for the Co(III) complex**

Co1–O1	1.9167 (10)	O1–Co1–O2	90.39 (4)
Co1–O2	1.9392 (10)	O1–Co1–N5	92.86 (5)
Co1–N5	1.9413 (12)	N6–Co1–O1	97.07 (5)
Co1–N6	1.8581 (12)	N6–Co1–O2	81.72 (5)
Co1–N1	1.9232 (12)	N6–Co1–N5	81.92 (5)
Co1–N2	1.8603 (12)	N6–Co1–N1	98.67 (5)
O1–C8	1.2987 (17)	N1–Co1–N5	90.20 (5)
O2–C21	1.2977 (17)	N2–Co1–O2	98.56 (5)
N2–Co1–N5	97.82 (5)	N2–Co1–N1	82.16 (5)
N2–Co1–O1	82.11 (4)	O1–Co1–N1	164.23 (5)
N1–Co1–O2	91.02 (5)	O2–Co1–N5	163.59 (5)
N6–Co1–N2	179.12 (5)		

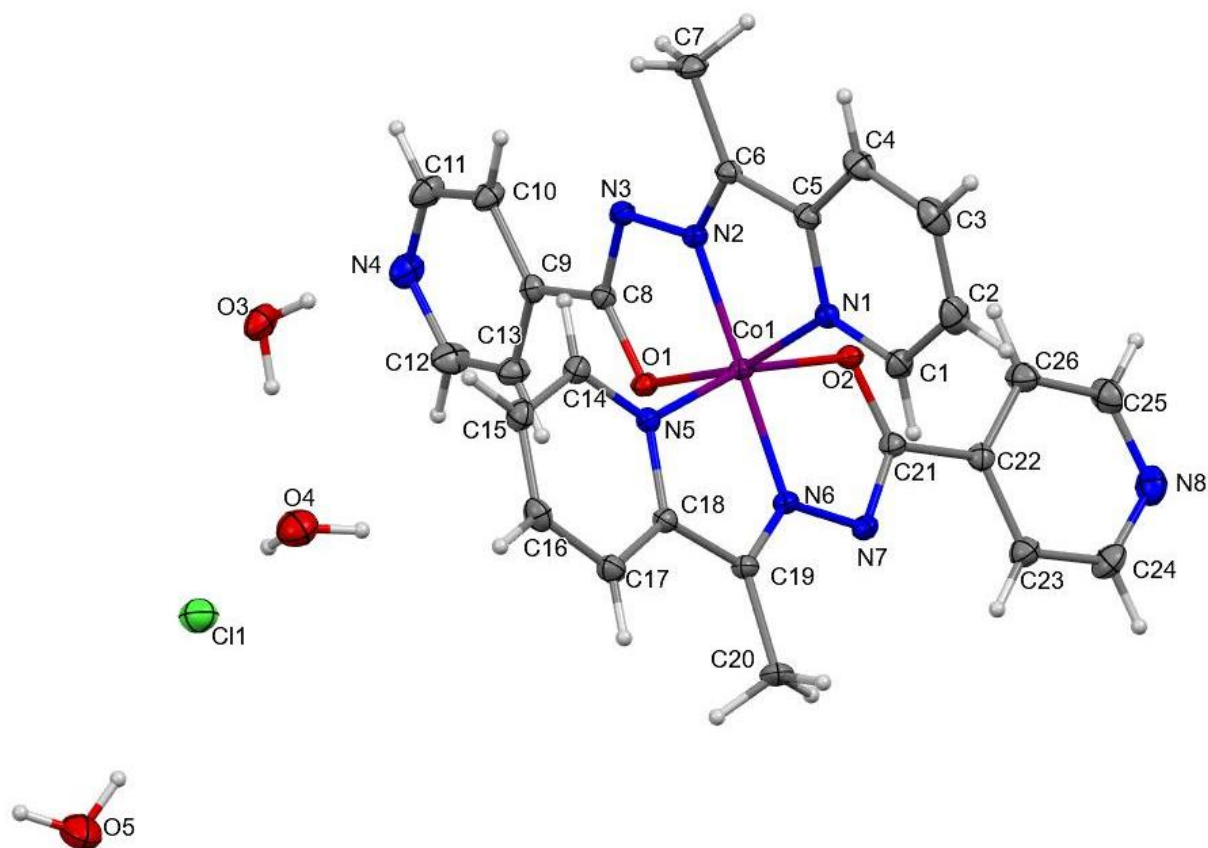
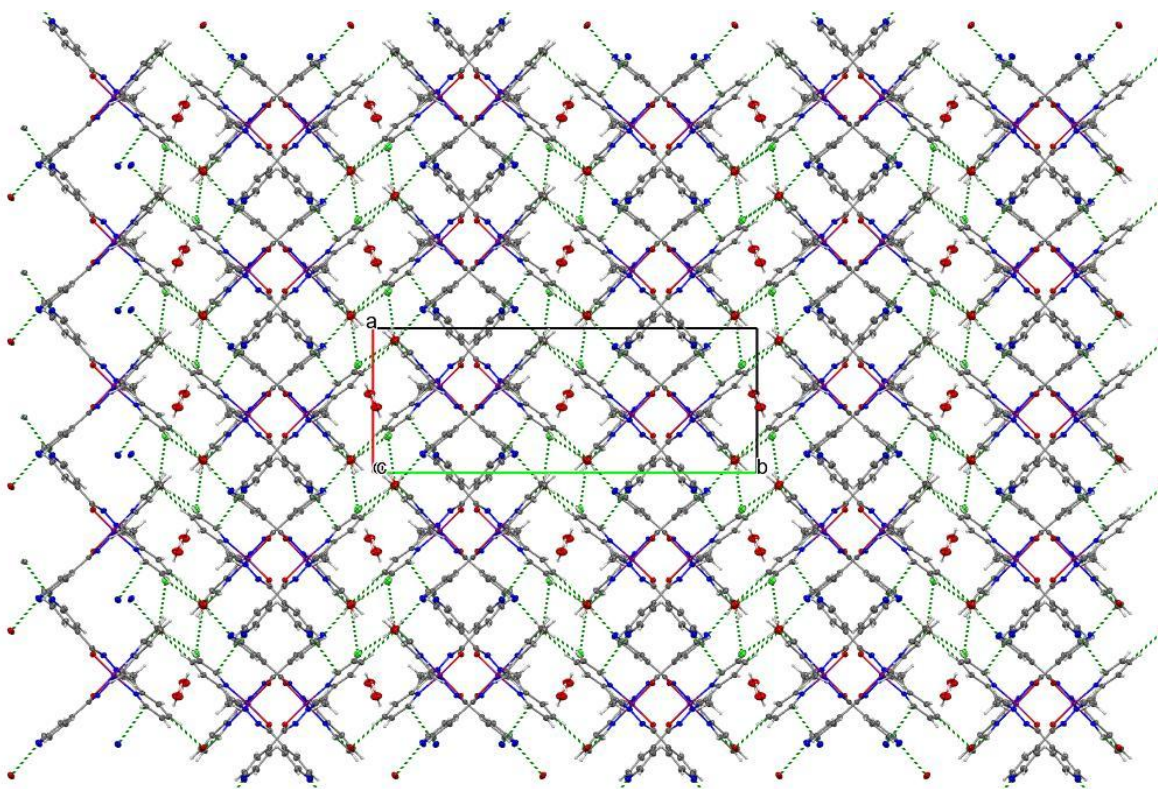


Figure 1 . Crystal structure of the complex  $[Co(HL)_2] \cdot Cl \cdot 3H_2O$  (1)

Table 3. Hydrogen-bond geometry ( $\text{\AA}$ ,  $^\circ$ ) for  $[Co(HL)_2] \cdot Cl \cdot 3H_2O$

D-H...A	D-H	H...A	D...A	D-H...A
C14-H14...N2	0.95	2.65	3.1213 (19)	110.8
C1-H1...N6	0.95	2.65	3.119 (2)	110.8
C1-H1...O3 <sup>i</sup>	0.95	2.27	3.056 (2)	139.6
C23-H23...O2 <sup>ii</sup>	0.95	2.64	3.385 (2)	135.3
C15-H15...Cl1 <sup>iii</sup>	0.95	2.95	3.6005 (17)	126.6
C4-H4...O4	0.95	2.57	3.445 (2)	153.1
C17-H17...O5 <sup>iv</sup>	0.95	2.54	3.484 (2)	170.8
C12-H12...Cl1 <sup>v</sup>	0.95	2.97	3.7156 (19)	136.5
C25-H25...Cl1 <sup>vi</sup>	0.95	2.95	3.7736 (18)	146.2

Symmetry codes: (i)  $x, y, z-1$ ; (ii)  $x, -y+3/2, z-1/2$ ; (iii)  $-x+1, -y+1, -z+1$ ; (iv)  $-x+1, -y+1, -z$ ; (v)  $-x+1, y+1/2, -z+1/2$ ; (vi)  $-x, y+1/2, -z+1/2$ .



**Figure 2. Packing diagram of the complex [Co(HL)<sub>2</sub>]-Cl·3H<sub>2</sub>O (1)**

#### 4. Conclusion

The complex [Co(HL)<sub>2</sub>]-Cl·3H<sub>2</sub>O synthesized by the reaction of the Schiff base *N*-(1-(pyridin-2-yl)ethylidene)isonicotinohydrazide (H<sub>2</sub>L) and hexahydrate cobalt dichloride have been characterized by IR and UV spectroscopies, conductivity and room temperature magnetic moment measurements and X-ray diffraction. Considering the conductance, the complex is stable in DMF solution. The complex is diamagnetic in nature indicating a high-spin cobalt (III) complex. The X-ray diffraction study shows that the Co(III) complex is mononuclear and the metal atom is situated in an octahedral geometry, surrounded by two molecules acting in tridentate ligand. The structure of complex is consolidated by extensive unclassical intermolecular hydrogen bonds of type C-H...N, C-H...O and C-H...Cl which produce a three-dimensional network in the solid.

#### 5. Supporting information

CCDC-2342789 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <https://www.ccdc.cam.ac.uk/structures/>, or by e-mailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

#### REFERENCES

1. Betancourth JG, Castaño JA, Visbal R, Chaur MN. Versatility of the Amino Group in Hydrazone-Based Molecular and Supramolecular Systems. *European Journal of Organic Chemistry*. 2022;28: e202200228. <https://doi.org/10.1002/ejoc.202200228>
2. Bismillah AN, Aprahamian, I. Boron Difluoride Hydrazone (BODIHY) Complexes: A New Class of Fluorescent Molecular Rotors. *Journal of Physical Organic Chemistry*. 2023;36:e4485. <https://doi.org/10.1002/poc.4485>
3. Gao P, Wei Y. Efficient oxidative cyclization of *N*-acylhydrazones for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles using *t*-BuOI under neutral conditions. *Heterocycle Communications*. 2013;19:113–119.

- <https://doi.org/10.1515/hc-2012-0179>
- Küçük BH, Alhonaish A, Yıldız T, Güzel M. An efficient approach to access 2,5-disubstituted 1,3,4-oxadiazoles by oxidation of 2-arenoxybenzaldehyde N- acyl hydrazones with molecular iodine. *ChemistrySelect*. 2022;7:e202201391. <https://doi.org/10.1002/slct.202201391>
  - Pelipko VV, Gomonov KA. Formation of five- and six-membered nitrogen-containing heterocycles on the basis of hydrazones derived from  $\alpha$ -dicarbonyl compounds (microreview). *Chemistry of Heterocycle Compounds*. 2021;57:624–626. <https://doi.org/10.1007/s10593-021-02958-8>
  - Morjan RY, Mkdadm AM, Beadham I, Elmanama AA, Mattar MR, Raftery J, Pritchard, RG, Awadallah AM, Gardiner JM. Antibacterial activities of novel nicotinic acid hydrazides and their conversion into N-acetyl-1,3,4-oxadiazoles. *Bioorganic & Medicinal Chemistry Letters*. 2014;24:5796–5800. <https://doi.org/10.1016/j.bmcl.2014.10.029>
  - Țiñțaș ML, Diac AP, Soran A, Terec A, Grosu I, Bogdan E. Structural characterization of new 2-aryl-5-phenyl-1,3,4-oxadiazin-6-ones and their N-arylhyazone precursors. *Journal of Molecular Structure*. 2014;1058:106–113. <https://doi.org/10.1016/j.molstruc.2013.11.005>
  - Wani MY, Bhat AR, Azam A, Athar F. Nitroimidazolyl hydrazones are better amoebicides than their cyclized 1,3,4-oxadiazoline analogues: In vitro studies and Lipophilic efficiency analysis. *European Journal of Medicinal Chemistry*. 2013;64:190–199. <https://doi.org/10.1016/j.ejmech.2013.03.034>
  - Belyaeva ER, Myasoedova YV, Ishmuratova NM, Ishmuratov GY. Synthesis and Biological Activity of N-Acylhydrazones. *Russian Journal of Bioorganic Chemistry*. 2022;48:1123–1150. <https://doi.org/10.1134/s1068162022060085>
  - Verma S, Lal S, Narang R, Sudhakar K. Quinoline Hydrazone/Hydrazone Derivatives: Recent Insights on Antibacterial Activity and Mechanism of Action. *ChemMedChem*. 2023;18:e202200571. <https://doi.org/10.1002/cmdc.202200571>
  - Lygaitis R, Getautis V, Grazulevičius JV. Hole-Transporting Hydrazones. *Chemical Society Reviews*. 2008;37:770–788. <https://doi.org/10.1039/B702406C>
  - Rollas S, Küçükgüzel, SG. Biological Activities of Hydrazone Derivatives. *Molecules* 2007;12:1910–1939. <https://doi.org/10.3390/12081910>
  - Mohareb RM, Ibrahim RA, Moustafa HE. Hydrazone-Hydrazones in the Synthesis of 1,3,4-Oxadiazine, 1,2,4-Triazine and Pyrazole Derivatives with Antitumor Activities. *The Open Organic Chemistry Journal*. 2010;4:8–14. <https://doi.org/10.2174/1874095201004010008>
  - García-Ramírez VG, Suarez-Castro A, Villa-Lopez MG, Díaz-Cervantes E, Chacón-García L, Cortes-García CJ. Synthesis of Novel Acylhydrazone-Oxazole Hybrids and Docking Studies of SARS-CoV-2 Main Protease. *Chemistry Proceedings*. 2020;3:1. <https://doi.org/10.3390/ecsoc-24-08329>
  - Aneja B, Khan NS, Khan P, Queen A, Hussain A, Rehman MT, Alajmi MF, El-Seedi HR, Ali S, Hassan MI, Abid M. Design, and development of Isatin-triazole hydrazones as potential inhibitors of microtubule affinity-regulating kinase 4 for the therapeutic management of cell proliferation and metastasis. *European Journal of Medicinal Chemistry*. 2019;163:840–852. <https://doi.org/10.1016/j.ejmech.2018.12.026>
  - Salum LB, Mascarello A, Canevarolo RR, Altei WF, Laranjeira ABA, Neuenfeldt PD, Stumpf TR, Chiaradia-Delatorre LD, Vollmer LL, Daghestani HN, de Souza Melo CP, Silveira AB, Leal PC, Frederico MJS, do Nascimento LF, Santos ARS, Andricopulo AD, Day BW, Yunes RA, Vogt A, Yunes JA, Nunes RJ. *N*-(1'-naphthyl)-3,4,5-trimethoxybenzohydrazone as microtubule destabilizer: Synthesis, cytotoxicity, inhibition of cell migration and in vivo activity against acute lymphoblastic leukemia. *European Journal of Medicinal Chemistry*. 2015;96:504–518. <https://doi.org/10.1016/j.ejmech.2015.02.041>

17. Govindaiah P, Dumala N, Mattan I, Grover P, Jaya Prakash M. Design, synthesis, biological and in silico evaluation of coumarin-hydrazone derivatives as tubulin targeted antiproliferative agents. *Bioorganic Chemistry*. 2019;91:103143. <https://doi.org/10.1016/j.bioorg.2019.103143>
18. Sreenivasulu R, Reddy KT, Sujitha P, Kumar CG, Raju RR. Synthesis, antiproliferative and apoptosis induction potential activities of novel bis(indolyl)hydrazide-hydrazone derivatives. *Bioorganic & Medicinal Chemistry*. 2019;27:1043–1055. <https://doi.org/10.1016/j.bmc.2019.02.002>
19. Sharma V, Kumar R, Bua S, Supuran CT, Sharma PK. Synthesis of novel benzenesulfonamide bearing 1,2,3-triazole linked hydroxy-trifluoromethylpyrazolines and hydrazones as selective carbonic anhydrase isoforms IX and XII inhibitors. *Bioorganic Chemistry*. 2019;85:198–208. <https://doi.org/10.1016/j.bioorg.2019.01.002>
20. Rohane SH, Chauhan AJ, Fuloria NK, Fuloria S. Synthesis and in vitro antimycobacterial potential of novel hydrazones of eugenol. *Arabian Journal of Chemistry*. 2020;13: 4495–4504. <https://doi.org/10.1016/j.arabjc.2019.09.004>
21. Siddique M, Bin Saeed A, Dogar NA, Ahmad S. Biological Potential of Synthetic Hydrazone Based Schiff Bases. *Journal of Scientific Innovative Research*. 2013;2:651–657. <http://www.jsirjournal.com/Vol2Issue3017.pdf>
22. Xia L, Xia Y.-F, Huang L.-R, Xiao X, Lou H.-Y, Liu T.-J, Pan W.-D, Luo H. Benzaldehyde Schiff bases regulation to the metabolism, hemolysis, and virulence genes expression in vitro and their structure–microbicidal activity relationship. *European Journal of Medicinal Chemistry*. 2015;97:83–93. <https://doi.org/10.1016/j.ejmech.2015.04.042>
23. Hincapié-Otero MM, Joaqui-Joaqui A, Polo-Cerón D. Synthesis and characterization of four *N*-acylhydrazones as potential O,N,O donors for Cu<sup>2+</sup>: An experimental and theoretical study. *Universitas Scientarum*. 2021;26:193–215. <https://doi.org/10.11144/Javeriana.SC26-2.saco>
24. Demurtas M, Baldisserotto A, Lampronti I, Moi D, Balboni G, Pacifico S, Vertuani S, Manfredini S, Onnis V. Indole derivatives as multifunctional drugs: Synthesis and evaluation of antioxidant, photoprotective and antiproliferative activity of indole hydrazones. *Bioorganic Chemistry*. 2019;85:568–576. <https://doi.org/10.1016/j.bioorg.2019.02.007>
25. Lis C, Rubner S, Roatsch M, Berg A, Gilcrest T, Fu D, Nguyen E, Schmidt A-M, Krautscheid H, Meiler J, Berg T. Development of Erasin: A chromone-based STAT3 inhibitor which induces apoptosis in Erlotinib-resistant lung cancer cells. *Scientific Reports*. 2017;7:17390. <https://doi.org/10.1038/s41598-017-17600-x>
26. Sun K, Peng J-D, Suo F-Z, Zhang T, Fu Y-D, Zheng Y-C, Liu H-M. Discovery of tranlycypromine analogs with an acylhydrazone substituent as LSD1 inactivators: Design, synthesis and their biological evaluation. *Bioorganic & Medicinal Chemistry Letters*. 2017;27: 5036–5039. <https://doi.org/10.1016/j.bmcl.2017.10.003>
27. Congiu C, Onnis V. Synthesis and biological evaluation of novel acylhydrazone derivatives as potential antitumor agents. *Bioorganic & Medicinal Chemistry*. 2013;21:6592–6599. <https://doi.org/10.1016/j.bmc.2013.08.026>
28. Cui Z, Li Y, Ling Y, Huang J, Cui J, Wang R, Yang X. New class of potent antitumor acylhydrazone derivatives containing furan. *European Journal of Medicinal Chemistry*. 2010;45:5576–5584. <https://doi.org/10.1016/j.ejmech.2010.09.007>
29. Li Y, Yan W, Yang J, Yang Z, Hu M, Bai P, Tang M, Chen L. Discovery of novel  $\beta$ -carboline/acylhydrazone hybrids as potent antitumor agents and overcome drug resistance. *European Journal of Medicinal Chemistry*. 2018;152:516–526. <https://doi.org/10.1016/j.ejmech.2018.05.003>
30. Socea L-I, Socea B, Saramet G, Barbuceanu S-F, Draghici C, Constantin VD, Olaru, OT. Synthesis and Cytotoxicity Evaluation of new 5H-dibenzo[a,d][7]annulen-5-yl acetylhydrazones. *Revista de Chimie*. 2015;66(8):1122–1127. <https://revistadechimie.ro/Articles.asp?ID=4591>

31. Bernhardt PV. Coordination Chemistry and Biology of Chelators for the Treatment of Iron Overload Disorders. *Dalton Transactions*. 2007;30:3214–3220.  
<https://doi.org/10.1039/b708133b>
32. He H, Xia H, Xia Q, Ren Y, He H. Design and optimization of N-acylhydrazone pyrimidine derivatives as *E. coli* PDHc E1 inhibitors: Structure-activity relationship analysis, biological evaluation and molecular docking study. *Bioorganic & Medicinal Chemistry*. 2017;25:5652–5661.  
<https://doi.org/10.1016/j.bmc.2017.08.038>
33. Jin Y-X, Zhong A-G, Ge C-H, Pan F-Y, Yang J-G, Wu Y, Xie M, Feng H-W. A novel difunctional acylhydrazone with isoxazole and furan heterocycles: Syntheses, structure, spectroscopic properties, antibacterial activities and theoretical studies of (*E*)-*N*-(furan-2-ylmethylene)-5-methylisoxazole-4-carbohydrazone. *Journal of Molecular Structure*. 2012;1010:190–196.  
<https://doi.org/10.1016/j.molstruc.2011.06.042>
34. Jin Y-X, Zhong A-G, Zhang Y, Pan F-Y. Synthesis, crystal structure, spectroscopic properties, antibacterial activity and theoretical studies of a novel difunctional acylhydrazone. *Journal of Molecular Structure*. 2011;1002:45–50.
35. Guilherme FD, Simonetti JÉ, Folquitto LRS, Reis ACC, Oliver JC, Dias ALT, Dias DF, Carvalho DT, Brandão GC, de Souza TB. Synthesis, chemical characterization, and antimicrobial activity of new acylhydrazones derived from carbohydrates. *Journal of Molecular Structure*. 2019;1184:349–356.  
<https://doi.org/10.1016/j.molstruc.2019.02.045>
36. Reis, D, Despaigne, A, Silva, J, Silva, N, Vilela, C, Mendes, I, Takahashi, J, Beraldo, H. Structural Studies and Investigation on the Activity of Imidazole-Derived Thiosemicarbazones and Hydrazones against Crop-Related Fungi. *Molecules* 2013;18:12645–12662.  
<https://doi.org/10.3390/molecules181012645>
37. Tian B, He M, Tang S, Hewlett I, Tan Z, Li J, Jin Y, Yang M. Synthesis, and antiviral activities of novel acylhydrazone derivatives targeting HIV-1 capsid protein. *Bioorganic & Medicinal Chemistry Letters*. 2009;19:2162–2167.  
<https://doi.org/10.1016/j.bmcl.2009.02.116>
38. Wang Z, Xie D, Gan X, Zeng S, Zhang A, Yin L, Song B, Jin L, Hu D. Synthesis, antiviral activity, and molecular docking study of trans-ferulic acid derivatives containing acylhydrazone moiety. *Bioorganic & Medicinal Chemistry Letters*. 2017;27:4096–4100.  
<https://doi.org/10.1016/j.bmcl.2017.07.038>
39. Inam A, Siddiqui SM, Macedo TS, Moreira DRM, Leite ACL, Soares MBP, Azam A. Design, synthesis, and biological evaluation of 3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propionic acid hydrazones as antiprotozoal agents. *European Journal of Medicinal Chemistry*. 2014;75:67–76.  
<https://doi.org/10.1016/j.ejmech.2014.01.023>
40. Melnyk P, Leroux V, Sergheraert C, Grellier P. Design, synthesis, and in vitro antimalarial activity of an acylhydrazone library. *Bioorganic & Medicinal Chemistry Letters*. 2006;16: 31–35.  
<http://dx.doi.org/10.1016/j.bmcl.2005.09.058>
41. dos Santos Filho JM, de Queiroz e Silva DMA, Macedo TS, Teixeira HMP, Moreira DRM, Challal S, Wolfender J-L, Queiroz EF, Soares MBP. Conjugation of *N*-acylhydrazone and 1,2,4-oxadiazole leads to the identification of active antimalarial agents. *Bioorganic & Medicinal Chemistry*. 2016;24:5693–5701.  
<https://doi.org/10.1016/j.bmc.2016.09.013>
42. Shakhdoifa MME, Shtaiwi MH, Morsy N, Abdel-rassel TMA. Metal complexes of hydrazones and their biological, analytical and catalytic applications: A review. *Main Group Chemistry*. 2014;13:187–218.  
<https://doi.org/10.3233/MGC-140133>
43. Dos Santos Filho, JM, Leite ACL, de Oliveira BG, Moreira DRM, Lima MS, Soares MBP, Leite LFCC. Design, synthesis and cruzain docking of 3-(4-substituted-aryl)-1,2,4-oxadiazole-*N*-acylhydrazones as anti-*Trypanosoma cruzi* agents. *Bioorganic & Medicinal Chemistry*. 2009;17:6682–6691.  
<https://doi.org/10.1016/j.bmc.2009.07.068>
44. Jacomini AP, Silva MJV, Silva RGM, Gonçalves DS, Volpato H, Basso EA, Paula FR, Nakamura CV, Sarragiotto MH, Rosa, FA. Synthesis and evaluation against *Leishmania*

- amazonensis of novel pyrazolo[3,4-d]pyridazinone-*N*-acylhydrazone-(bi)thiophene hybrids. *European Journal of Medicinal Chemistry*. 2016;124:340–349.  
<https://doi.org/10.1016/j.ejmech.2016.08.048>
45. Bezerra-Netto HJC, Lacerda DI, Miranda ALP, Alve, HM, Barreiro EJ, Fraga CAM. Design and synthesis of 3,4-methylenedioxy-6-nitrophenoxyacetylhydrazone derivatives obtained from natural safrole: New lead-agents with analgesic and antipyretic properties. *Bioorganic & Medicinal Chemistry*. 2006;14:7924–7935.  
<https://doi.org/10.1016/j.bmc.2006.07.046>
  46. Duarte CD, Tributino JLM, Lacerda DI, Martins MV, Alexandre-Moreira MS, Dutra F, Bechara EJJ, De-Paula FS, Goulart MOF, Ferreira J, Calixto JB, Nunes MP, Bertho AL, Miranda ALP, Barreiro EJ, Fraga CAM. Synthesis, pharmacological evaluation and electrochemical studies of novel 6-nitro-3,4-methylenedioxyphenyl-*N*-acylhydrazone derivatives: Discovery of LASSBio-881, a new ligand of cannabinoid receptors. *Bioorganic & Medicinal Chemistry*. 2007;15:2421–2433.  
<https://doi.org/10.1016/j.bmc.2007.01.013>
  47. Hernández P, Cabrera M, Lavaggi ML, Celano L, Tiscornia I, Rodrigues da Costa T, Thomson L, Bollati-Fogolín M, Miranda ALP, Lima LM, Barreiro EJ, González M, Cerecetto H. Discovery of new orally effective analgesic and anti-inflammatory hybrid furoxanyl *N*-acylhydrazone derivatives. *Bioorganic & Medicinal Chemistry*. 2012;20:2158–2171.  
<https://doi.org/10.1016/j.bmc.2012.01.034>
  48. Guimaraes ET, dos Santos TB, Silva DKC, Meira CS, Moreira DRM, da Silva TF, Salmon D, Barreiro EJ, Soares MBP. Potent immunosuppressive activity of a phosphodiesterase-4 inhibitor *N*-acylhydrazone in models of lipopolysaccharide-induced shock and delayed-type hypersensitivity reaction. *International Immunopharmacology*. 2018;65:108–118.  
<https://doi.org/10.1016/j.intimp.2018.09.047>
  49. Özer ÖE, Tan UO, Ozadali K, Küçükilingç T, Balkan A, Uçar G. Synthesis, molecular modeling and evaluation of novel *N*-2-(4-benzylpiperidin-/piperazin-1-yl)acylhydrazone derivatives as dual inhibitors for cholinesterases and A $\beta$  aggregation. *Bioorganic & Medicinal Chemistry Letters*. 2013;23:440–443.  
<https://doi.org/10.1016/j.bmcl.2012.11.064>
  50. Parlar S, Sayar G, Tarikogullari AH, Karadagli SS, Alptuzun V, Erciyas E, Holzgrabe U. Synthesis, bioactivity and molecular modeling studies on potential anti-Alzheimer piperidinehydrazide-hydrazones. *Bioorganic Chemistry*. 2019;87:888–900.  
<https://doi.org/10.1016/j.bioorg.2018.11.051>
  51. Anastassova NO, Yancheva DY, Mavrova AT, Kondeva-Burdina MS, Tzankova VI, Hristova-Avakumova NG, Hadjimitova VA. Design, synthesis, antioxidant properties and mechanism of action of new *N,N'*-disubstituted benzimidazole-2-thione hydrazone derivatives. *Journal of Molecular Structure*. 2018;1165:162–176.  
<https://doi.org/10.1016/j.molstruc.2018.03.119>
  52. Socea LI, Visan DC, Barbuceanu SF, Apostol TV, Bratu OG, Socea B. The Antioxidant Activity of Some Acylhydrazones with Dibenzo annulene Moiety. *Revista de Chimie*. 2018;69:795–797.  
<https://doi.org/10.37358/RC.18.4.6202>
  53. Tariq Q-N, Malik S, Khan A, Naseer MM, Khan SU, Ashraf A, Ashraf M, Rafiq M, Mahmood K, Tahir MN, Shafia Z. Xanthenone-based hydrazones as potent  $\alpha$ -glucosidase inhibitors: Synthesis, solid state self-assembly and in silico studies. *Bioorganic Chemistry*. 2019;84:372–383.  
<https://doi.org/10.1016/j.bioorg.2018.11.053>
  54. Shakdofa MME, Shtaiwi MH, Morsy N, Abdel-rassel TMA. Metal complexes of hydrazones and their biological, analytical and catalytic applications: A review. *Main Group Chem*. 2014;13:187–218.  
<https://doi.org/10.3233/MGC-140133>
  55. Shaikh I, Jadeja RN, Patel R, Mevada V, Gupta VK. 4 Acylhydrazone-5-Pyrazolones and their Zinc(II) Metal Complexes: Synthesis, Characterization, Crystal Feature and Antimalarial Activity *J. Mol. Struct.*, 2021;1232:130051.  
<https://doi.org/10.1016/j.molstruc.2021.130051>

56. Huang D-S, Liu X-R, Zhao S-S, Yang Z-W. Crystal structures of three transition metal complexes with salicylaldehyde-4-hydroxy phenylacetyl acylhydrazone and their interactions with CT-DNA and BSA, *Polyhedron*. 2022;211(1):115516.  
<https://doi.org/10.1016/j.poly.2021.115516>
57. Huang X, Yan S-Y, Chen Y-M, Zhang D-S, Huang C, Zhu B-X, Lu J-H. Synthesis, structures, and gas adsorption properties of Hg(II) and Cd(II) complexes constructed from two acylhydrazone ligands with multiple coordination sites *Inorganica Chimica Acta*. 2023;555:121588.  
<https://doi.org/10.1016/j.ica.2023.121588>
58. Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JAK, Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. *Journal of Applied Crystallography*. 2009;42(2):339-341.  
<https://doi.org/10.1107/S0021889808042726>
59. Sheldrick GM. SHELXT – Integrated space-group and crystal-structure determination. *Acta Crystallographica*. 2015;A71(1):3-8.  
<https://doi.org/10.1107/S2053273314026370>
60. Sheldrick GM. Crystal structure refinement with SHELXL. *Acta Crystallographica*. 2015;C71(1):3-8.  
<https://doi.org/10.1107/S2053229614024218>
61. Farrugia LJ. WinGX and ORTEP for Windows: an update, *Journal of Applied Crystallography*. 2012;45:849-854.  
<https://doi.org/10.1107/S002188981202911>
62. Tariq Q-N, Malik S, Khan A, Naseer MM, Khan SU, Ashraf A, Ashraf M, Rafiq M, Mahmood K, Tahir MN, Shafia Z. Xanthenone-based hydrazones as potent  $\alpha$ -glucosidase inhibitors: Synthesis, solid state self-assembly and in silico studies. *Bioorganic Chemistry*. 2019;84:372–383.  
<https://doi.org/10.1016/j.bioorg.2018.11.053>
63. Kuriakose D, Kurup MRP. Crystal structures and supramolecular architectures of ONO donor hydrazone and solvent exchangeable dioxidomolybdenum(VI) complexes derived from 3,5-diiodosalicylaldehyde-4-methoxybenzoylhydrazone: Hirshfeld surface analysis and interaction energy calculations, *Polyhedron*. 2019;170:749–761.  
<https://doi.org/10.1016/j.poly.2019.06.041>
64. Geary WJ. The use of conductivity measurements in organic solvents for the characterisation of coordination compounds. *Coordination Chemistry Reviews*. 1971;7(1):81-122.  
[https://doi.org/10.1016/S0010-8545\(00\)80009-0](https://doi.org/10.1016/S0010-8545(00)80009-0)
65. Mathews NA, Jose A, Kurup MRP. Synthesis and characterization of a new aroylhydrazone ligand and its cobalt(III) complexes: X-ray crystallography and in vitro evaluation of antibacterial and antifungal activities, *Journal of Molecular Structure*. 2019;1178:544–553 .  
<https://doi.org/10.1016/j.molstruc.2018.10.061>
66. Das M., Chattopadhyay S. Synthesis, and structures of two cobalt(III) complexes with N4 donor ligands: Isolation of a unique bishemiaminal ether ligand as the metal complex, *Polyhedron*. 2013;50:443–451.  
<http://dx.doi.org/10.1016/j.poly.2012.11.025>
67. Buvaylo EA, Kasyanova KA, Yu O, Vassilyeva BW, Skelton. Crystal structure of bis{4-bromo-2-[(carbamimidamidoimino)-methyl]phenolato- $\kappa^3 N, N', O$ }cobalt(III) nitrate dimethyl formamide monosolvate, *Acta Crystallographica*. 2016;E72:907–911.  
<https://doi.org/10.1107/S2056989016008690>