https://doi.org/10.48048/tis.2022.1500

Synthesis, Structural Studies and Antimicrobial Evaluation of Nickel(II) Bis-Complex of Schiff Base of S-Benzyldithiocarbazate

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Received: 23 December 2021, Revised: 23 January 2022, Accepted: 31 January 2022, Published: 9 November 2022

Abstract

A tridentate nitrogen-oxygen-sulfur (NOS) S-benzyl(2-oxoindolin-3-ylidene)dithiocarbazate, HSBISA (**HL1**) ligand was synthesized via a condensation reaction between S-benzylditihocarbazate (SBDTC) and isatin. The produced ligand was reacted with nickel(II) acetate salt in 1:2 (metal:ligand) ratio to yield a brown $Ni(SBISA)_2$ complex (**2**) (SBISA = monoanionic form of **HL1**). Characterization of **HL1** and its Ni(II) complex was performed via elemental analysis, FT-IR, ICP-AES, UV-Vis spectroscopy and mass spectrometry, along with molar conductivity and magnetic susceptibility measurement. Slow evaporation of **2** from DMSO at room temperature led to a structure crystallizing in the monoclinic $P2_1/a$ space group with a = 18.6860(3), b = 11.3037(2), c = 19.8993(3), β = 112.1897(10), V = 3891.86(11) $Å^3$, wR_2 (all data) = 0.0407 and R_1 = 0.0386 for data with $I > 2\sigma(I)$. The nickel(II) metal center is ligated by doubly-deprotonated NOS monoanionic tridentate **HL1** ligands forming a neural distorted octahedral $Ni(SBISA)_2 \cdot 2DMSO$ (**2a**) complex. The antimicrobial assays of both compounds were performed on selected pathogenic bacteria and fungi strains.

Keywords: Nickel(II), Dithiocarbazate, Isatin, Nickel acetate tetrahydrate, Crystal structure, Antimicrobial

Introduction

The coordination chemistry of dithiocarbazates Schiff base ligands derived from heterocyclic compounds continues to be of interest because of their versatile coordination ability and significant role in various fields [1-6]. Dithiocarbazate has a general structure of $R\text{-}CS_2NHNH_2$, where R is organic alkyl, aryl or heteroaromatic group. Due to the presence of the terminal amino NH_2 group, many researchers have utilized dithiocarbazate in the construction of important organic compounds such as imines, pyrazoline, pyrazole, and thiadiazoles [7-11]. Among the aforementioned compounds, imines containing isatin scaffolds have attracted enormous interest as it can form stable complexes with variable denticity towards metal ions [12-15]. Isatin is an indole heterocyclic natural product found in some plant species and has been found to exhibit diverse pharmacological activities including antibacterial and antifungal capabilities [16-20]. The increasing microbial resistance to antimicrobial drugs necessitates the discovery and development of new compounds. Such strategy includes designing a metal-based compound that specifically attack and eradicates a target microorganism in order to prevent its pathogenesis [21]. Metal complexes of isatin based ligands play a vital role in medicinal chemistry as they exhibit broad spectrum of geometries, oxidation numbers and valencies, all of which modulate the biological properties of designed compounds [22-24]. Nickel is present naturally in a few classes of proteins such as urease, carbon monoxide dehydrogenase and Ni/Fe hydrogenase [25]. Recently, several nickel complexes containing isatin moiety have been evaluated for their antimicrobial activities [26-28]. Dar *et al*. [27] synthesized series of transition metal complexes of isatin dibenzoylmethane mixed ligand compounds and assessed their antifungal activities against *Candida albicans*. The nickel(II) complex was found to exert potent antimicrobial activities against these tested strains. The mechanism of action is suggested to proceed via the induced apoptosis in *Candida albicans* and therefore has the potential to overcome issues pertaining to antimicrobial drug resistance [27]. In a related study, Jain and Singh [28] have constructed a series of metal complexes of isatin tetraaza macrocyclic via a template method and evaluated their antimicrobial activity. Among complexes synthesized, the chlorinated nickel(II) compound was found to be the most effective for inhibiting *Candida albicans* and *Saccharomyces cerevisiae* growth [28].

Moreover, according to FDA databases, indole and its derivatives have been classified as one of the top 25 approved drugs for the treatment of various disorders and diseases [29]. Inspired by pharmacological implications of both dithiocarbazate and isatin moieties, as well as data from our previous work, reported herein are the preparation, characterization, antimicrobial evaluation and structural studies of nickel(II) complex of isatin dithiocarbazate.

Materials and methods

All reagents and solvents were purchased at analytical grade from commercial sources (Sigma-Aldrich, Fluka and Merck) and were used without purification. Melting points were determined with an Electrothermal IA9100 digital point apparatus and are uncorrected. Elemental analysis (C, H, N and S) was obtained using LECO CHNS-932 elemental analyzer (LECO, Saint Joseph, MI, USA). Mass spectrum of HBISA was recorded using a Shimadzu Gas Chromatography-Mass Spectrometer (GCMS-QP5050A) using direct injection (DI-MS) technique. The percentage of nickel content of $Ni(SBISA)_2$ (**2**) was measured using a Perkin-Elmer Plasma 1000 Emission Spectrometer. Infrared spectra were measured between 4,000 - 400 cm^{-1} using the potassium bromide (KBr) pellet with Perkin–Elmer FT IR 1750X spectrophotometer. Conductance measurement was conducted at room temperature on freshly prepared 10^{-3} DMSO solution using a Jenway 4310 conductivity meter fitted with a dip-type cell with a platinized electrode. The magnetic study of $Ni(SBISA)_2$ (**2**) was carried out at room temperature using a Sherwood Scientific MSB-AUTO magnetic susceptibility balance calibrated with $Hg[Co(SCN)_4]$. UV-Vis spectra were recorded with a Shimadzu UV-2501 PC Recording Spectrophotometer in the 200 - 1,000 nm region.

Synthesis of S-benzyl(2-oxoindolin-3-ylidene)dithiocarbazate, HSBISA (HL1)

The ligand precursor, S-benzyldithiocarbazate (SBDTC) and HSBISA were synthesized by literature method [30,31]. Isatin (735 mg, 5 mmol) was dissolved in hot ethanol (95 %) (10 mL) then added gradually to an equimolar amount of SBDTC (990 mg, 5 mmol) dissolved in hot ethanol (95 %) (10 mL). The reaction mixture was heated at 80 ℃, stirred for 20 min and allowed to stand at room temperature for 30 min. The resulting yellowish solid formed was separated, filtered and washed with cold ethanol. The product was recrystallized from ethanol and dried under vacuum. Yield 1.40 g, 81 %. The melting point and NMR spectroscopic data matched that in the literature [30,31]. Selected IR (KBr pellet, cm^{-1}) ν(C=O) 1696; ν(C=N) 1618; ν(N-N) 1104; ν (C=S) 1068. UV-Vis [λ_{max}, DMSO, nm (Log ε mol^{-1} l cm^{-1})]: 263(3.98), 385(4.15) and 449 (4.06). MS: $[M]^+$ at m/z 327.

Synthesis of bis-[S-benzyl(2-oxoindolin-3-ylidene)dithiocarbazato]nickel(II), $Ni(SBISA)_2$ (2)

Nickel acetate tetrahydrate (62 mg, 0.25 mmol) dissolved in hot 95 % ethanol (4 mL) was added slowly to a solution of **HL1** (164 mg, 0.5 mmol) in 5 mL of hot ethanol (95 %). The brownish solution was heated at 80 ℃ with constant stirring for 20 min. The resulting solution was concentrated and allowed to cool to room temperature (25 ℃). The brownish precipitate formed was separated by filtration, washed thoroughly with ethanol and dried in vacuum over anhydrous silica gel to afford the pure complex. Yield 139 mg, 78 %. m.p 247 - 248 ℃. Anal. Calc. for $C_{32}H_{24}N_6NiO_2S_4$ required: C, 54.02; H, 3.40; N, 11.81; S, 18.03; Ni, 8.25. Found: C, 53.96; H, 3.42; N, 11.56; S, 17.97; Ni, 7.97 %. Selected IR data (KBr pellet, cm^{-1}) ν(C=O) 1680; ν(C=N) 1602; ν(N-N) 1056; ν(C-S) 994. UV-Vis spectrum [λ_{max}, DMSO, nm (Log ε mol^{-1} l cm^{-1})] 263(4.59), 386(4.50), 476(4.34), ≈550sh, 938(1.93). μ_{eff} = 3.75 B.M. Λ (DMSO, 10^{-3} Ω^{-1} cm^2 mol^{-1}): 4.1. Dark green crystals of $Ni(SBISA)_2 \cdot 2DMSO$ (**2a**) suitable for X-ray work were obtained by slow evaporation of a DMSO solution.

X-ray structure determination of 2a

X-ray diffraction data were acquired at 150 K using the Enraf-Nonius Kappa CCD diffractometer equipped with a graphite-monochromatic Mo Kα radiation (λ = 0.71073 Å). Intensity data were processed using the DENZO-SMN package [32]. The structure was solved using the direct-methods program SIR92 [33] and refined by full-matrix least-squares technique based on F with CRYSTALS Program Suite [34]. Molecular structure of 2a was drawn using Mercury 4.2.0 software [35]. Deposition number **768275** contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Crystal data. $C_{36}H_{34}CdF_2N_6O_4S_6$, M = 867.83, monoclinic, a = 18.6860(3), b = 11.3037(2), c = 19.8993(3) Å, β = 112.1897(10) °, V = 3891.86(11) $Å^3$, T = 150 K, space group $P2_1/a$, Z = 4, 16748

reflections measured, 8870 unique (R_{int} = 0.027), which were used in all calculations. The final R_1 [$I > 2\sigma(I)$] and wR_2 (all data) were 0.0386 and 0.0407, respectively.

Qualitative antimicrobial assay

The antimicrobial activity of **HL1** and its nickel(II) complex (**2**) were assayed *in vitro* by measuring the inhibition zones (mm) against both Gram-positive (methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacillus subtilis*, Gram-negative bacteria (*Pseudomonas aeruginosa*, *Salmonella choleraesuis*) and fungi strains (*Candida albicans*, *Aspergillus ochraceous*, *Saccharomyces cerevisiae*) in order to evaluate their antimicrobial potential. The cultures were prepared using the disc diffusion technique as previously described [36]. Briefly, a lawn of microorganisms was prepared by pipetting and evenly spreading inoculum (10^{-4} mL, adjusted turbidometrically to 10^5 - 10^6 cfu/mL (cfu: colony forming units) onto nutrient agar set in Petri dishes. A sterilized filter paper discs (Whatman No. 1, 6 mm diameter) impregnated with a stock solution of each compound (100 mg/mL) in DMSO was allowed to dry before it was transferred onto the inoculated agar plates and incubated at 37 °C in a 5 % CO_2 enriched atmosphere for 24 h.

Results and discussion

Mass spectrum analysis of HL1

The mass spectrum of **HL1** is shown in **Figure 1** and its molecular ion is characterized by a peak m/z $[M]^+$ 327. The first fragmentation with m/z value of 299 was due to the loss of the CO group of the isatin moiety [37]. Further fragmentation of this molecular ion, gave rise to m/z 182, 117 and 90 peaks, respectively and are shown in **Scheme 1**.

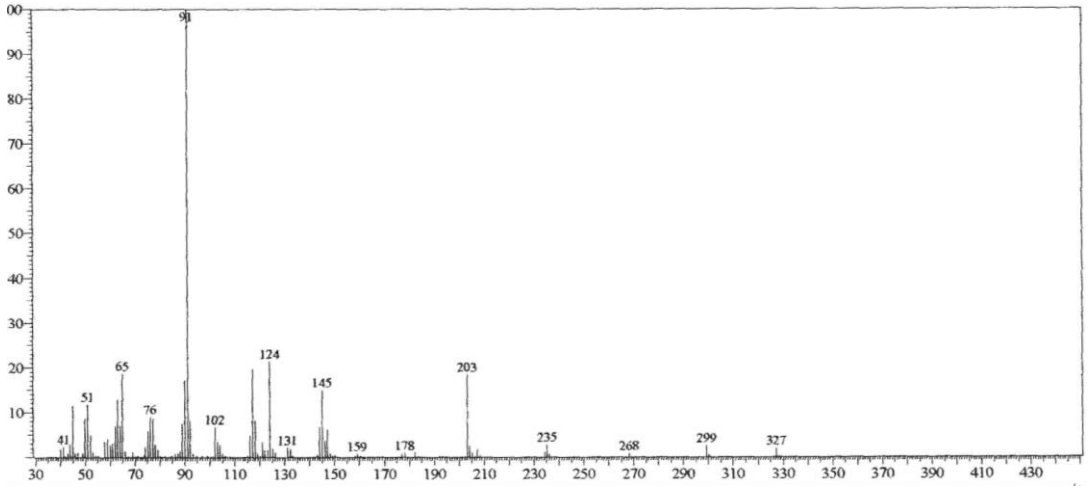
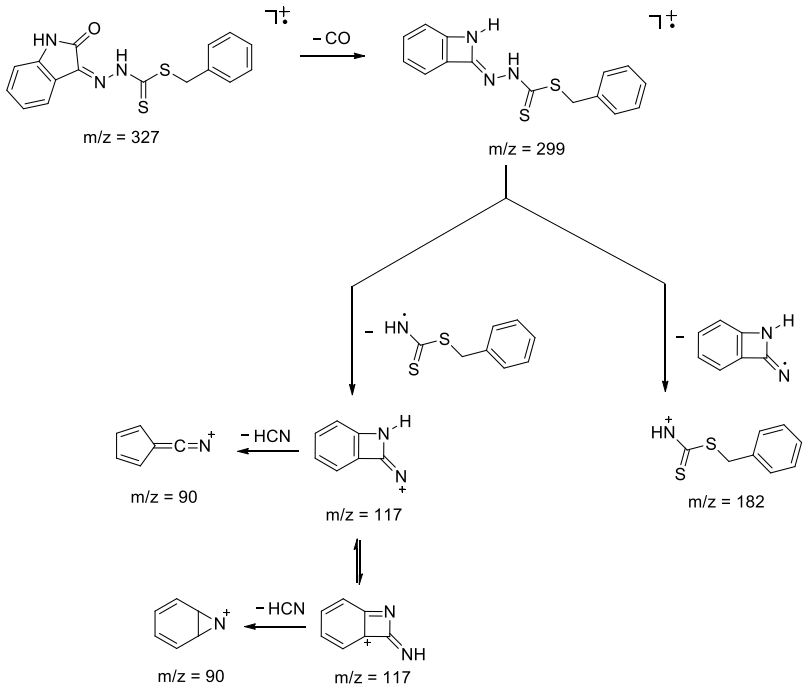
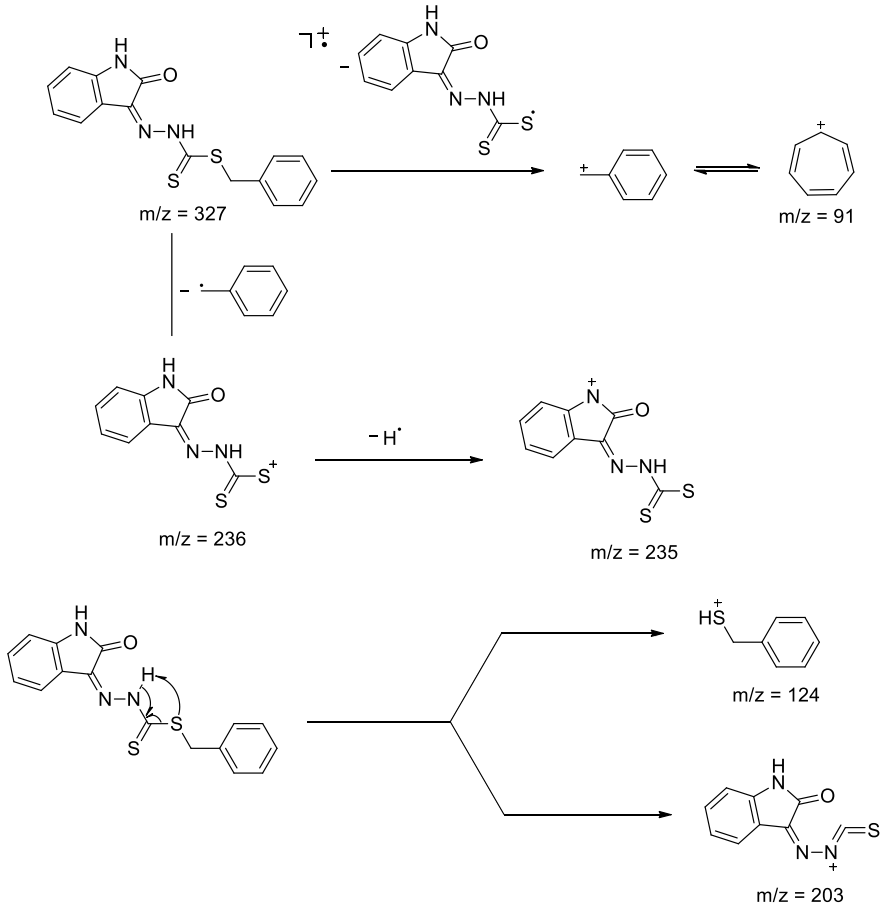


Figure 1 Mass spectrum of **HL1**.



Scheme 1 Fragmentation ions of **HL1** observed at m/z 182, 117 and 90.

In addition, 3 characteristic peaks were observed for **HL1**. These peaks appeared at m/z = 124, 203 and 235 are due to the fragmentation of the S-benzyldithiocarbazate and the isatin moieties, respectively. The base peak corresponds to the benzyl carbocation which then rearranged to more stable tropylium ion was observed at m/z = 91 [38]. The fragmentation patterns are shown in **Scheme 2**.



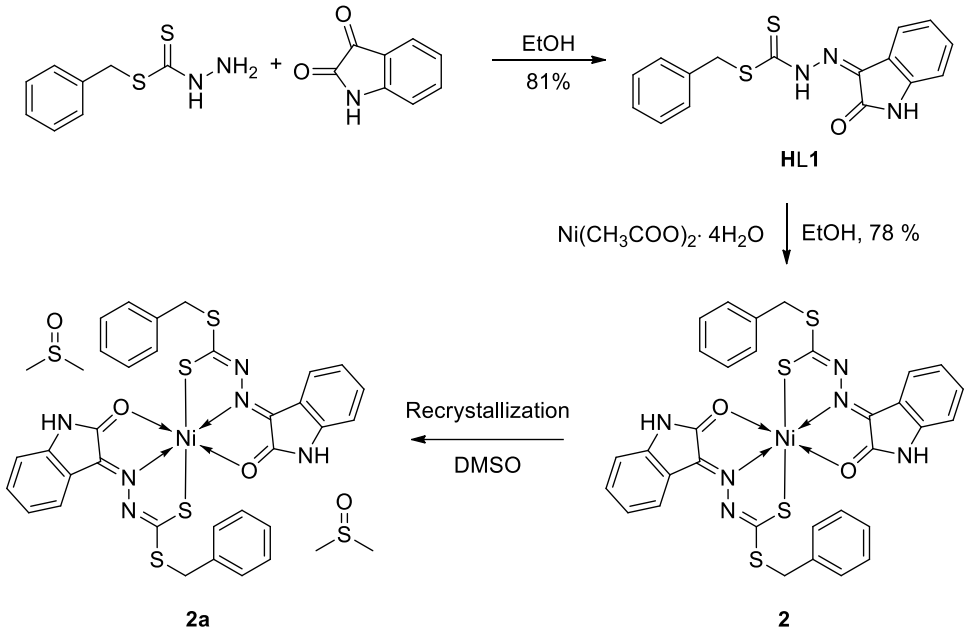
Scheme 2 Fragmentation ions of **HL1** observed at m/z 235, 203, 124 and 91.

Spectroscopic and physical characterization of 2

Formation of the bis-[S-benzyl(2-oxoindolin-3-ylidene)dithiocarbazato]nickel(II) complex (**2**), is shown in the following equation:

$Ni(OAc)_2{\cdot}4H_2O + 2HSBISA \rightarrow [Ni(SBISA)_2] + 2CH_3COOH + 4H_2O$; (OAc = acetate)

HL1 reacts with $Ni(OAc)_2{\cdot}4H_2O$ and forms brown precipitate in ethanol solution. During the course of reaction, **HL1** undergoes tautomerization and converted into the corresponding thiolate moiety in the presence of Ni(II) acetate. The synthesis method established for the preparation of **2** in this work is slightly different from the study reported earlier [31]. The present route is relatively simple, convenient, straight forward and could proceed easily without exclusion of air and moisture. $Ni(SBISA)_2$ (**2**) was non-hygroscopic, stable in air and its purity was identified via elemental analyses, which led to the postulated $Ni(SBISA)_2$ empirical formula. Recrystallization of **2** in DMSO afforded crystalline complex **2a** and its structural elucidation was performed by means of single crystal X-ray diffraction. The synthetic route leading to the title compounds **HL1** and **2** is illustrated in **Scheme 3**.

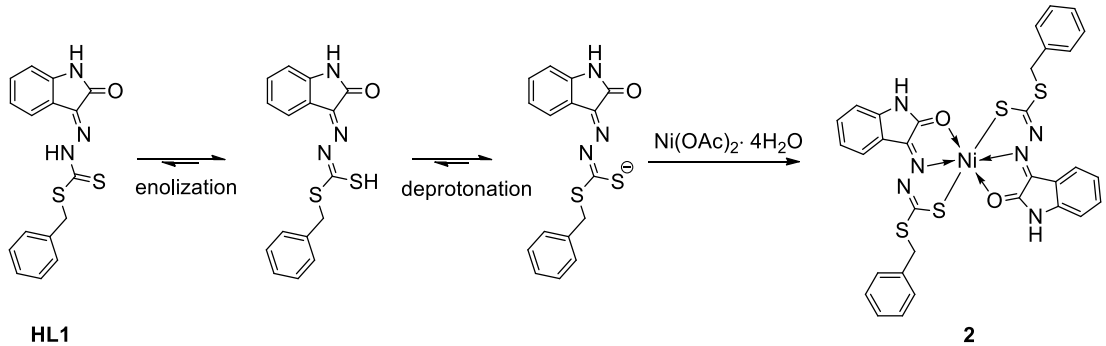


Scheme 3 Synthesis of **HL1** and complex **2**.

In the FT-IR spectrum of **HL1**, the stretching vibration of the (C=S) thione group, appearing at 1,068 cm^{-1} is not present in the spectrum of complex **2**, suggesting enolization followed by deprotonation before the coordination of the sulfur atom to the metal ion (**Scheme 4**). This coordination mode is further supported by the presence of a new C-S stretching frequency at 994 cm^{-1}. Additionally, bands corresponding to both azomethine C=N (1,618 cm^{-1}) and carbonylic C=O (1,696 cm^{-1}) of **HL1** free ligand are shifted to lower frequencies of 1,602 and 1,680 cm^{-1}, respectively in the spectrum of **2** (**Table 1**) are evidence for the nitrogen and oxygen atoms coordination [15,31]. Another evidence of the azomethine coordination is observed through the shift of the N-N band to lower frequency (1,056 cm^{-1}) regards to the free ligand (1,104 cm^{-1}) [39].

Table 1 IR spectra of **H1** and **2**.

Compound	Band (wavelength, cm^{-1})				
	ν(C=O)	**ν(C=N)**	**ν(C=S)**	**ν(C-S)**	**ν(N-N)**
HL1	1,696	1,618	1,068	-	1,104
2	1,680	1,602	-	994	1,056



Scheme 4 Enolization followed by deprotonation of **HL1** prior to coordination to nickel(II).

Table 2 demonstrates the electronic spectral data of **HLl** and its Ni(II) complex (**2**)**,** where **HL1** exhibits 3 prominent intraligand peaks at 262, 385 and 449 nm. Bands at 262 and 385 nm are assigned to $\pi\rightarrow\pi^*$ transitions of the phenyl ring of the dithiocarbazate and isatin moieties, while band at 449 nm is attributed to $n\rightarrow\pi^*$ transition of the carbonylic, thione and azomethine chromophores, respectively. Similar intraligand transitions were also observed in a related structure containing isatin analogues [40,41]. The appearance of a S→Ni(II) ligand to metal charge transfer (LMCT) transition in the spectrum of $Ni(SBISA)_2$ at 474 nm suggests a strong evidence that the dithiocarbazate sulfur atom is involved in the coordination. Furthermore, 2 low energy *d-d* transitions appeared at 938 and 550 nm assigned to $^3A_{2g}\rightarrow{}^3T_{2g}(F)$ and $^3A_{2g}\rightarrow{}^3T_{1g}(F)$, respectively indicating to an octahedral geometry complex. The magnetic moment of complex **2** reported herein exhibits a value of 3.75 B.M., which falls within the range of normal of octahedral Ni(II) complexes [42-44]. The molar conductivity value of **2** is 4.1 implies the absence of counter ion outside of the coordination sphere and its non-electrolytic character [45].

Table 2 UV-Vis spectral, molar conductance and magnetic moment data of **HL1** and **2**.

Compound	UV-Vis spectra bands λ_{max}, nm (Log ε, mol^{-1} l cm^{-1})	Conductance Ω^{-1} cm^2 mol^{-1}	μ_{eff} B.M.
HL1	262(3.98), 385(4.15), 449(4.06)	-	-
2	263(4.59), 386(4.50), 474(4.34), ≈550sh, 938(1.93)	4.1	3.75

Structural analysis of 2a

ORTEP representation of **2a** showing selective atom labeling scheme is shown in **Figure 1**. The structural asymmetric unit is composed of a Ni(II) complex molecule and two DMSO solvent molecules, with both ligands are independent and not symmetrically related. The Ni(II) atom is hexacoordinated in an octahedral coordination, being surrounded by 2 N, O and S thiolate atoms from 2 N,O,S-tridentate SBISA ligands. The 2 azomethine nitrogen atoms around the metal center are trans to each other, with an N-Ni-N bond angle of 169.03 °, while the thiolate sulfur and carbonylic oxygen atoms are oriented in cis configurations with bond angles of S-Ni-O of 93.03 and 91.11 °, respectively. The bond angles N13-N1-N35 (169.03 °), S24-Ni1-N35 (81.07 °), N35-Ni1-O38 (79.98 °), S2-Ni1-N13 (80.74 °) and N13-Ni1-O23 (80.49 °) deviate from the ideal values of 180 and 90 °, respectively, revealing the distortion of a planar geometry.

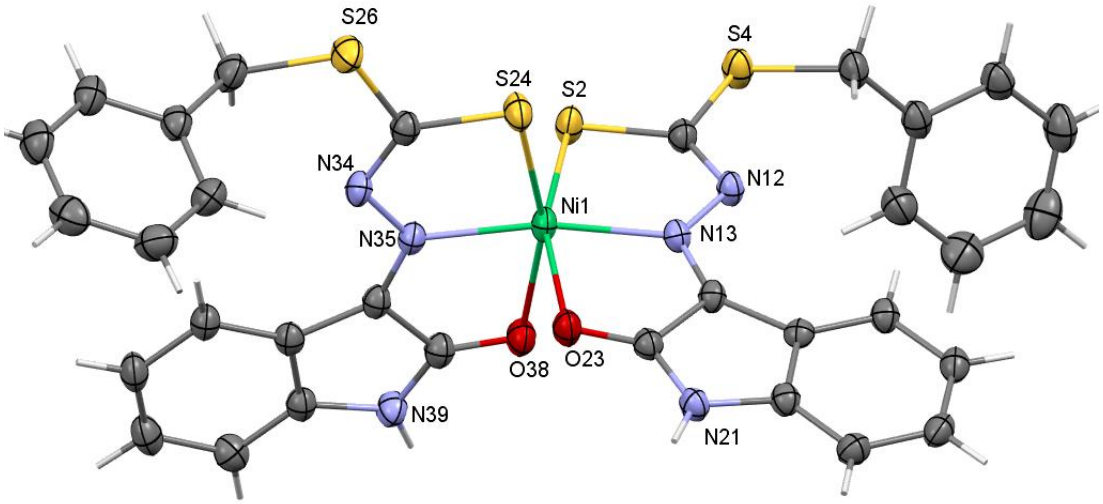


Figure 1 Crystal structure of complex **2a** (50 % probability ellipsoids). The DMSO molecules are omitted for clarity.

The individual ligand bite angles [S24-Ni1-O38 160.96 °, S2-Ni1-O23 160.76 °] were similar to those seen in the related complexes $[Ni(isasbz)_2\cdot DMSO]$ (159.55 °), $[Ni(isa\text{-}sme)_2\cdot MeCN]$ (158.06 and 160.40 °), $[Ni(isaPhTSC)_2]$ (160.58 and 161.23 °), $[Ni(isaTSC)_2\cdot 2DMF]$ (156.47 and 161.35 °)(and

[Ni(isaTSC)$_2$·EtOH] (161.36 °) (isasbz = anion of S-benzyl(2-oxoindolin-3-ylidene)dithiocarbazate, isa-sme = anion of S-methyl(2-oxoindolin-3-ylidene)dithiocarbazate, isaPhTSC = anion of (Z)-2-(1-allyl-2-oxoindolin-3-ylidene)-*N*-phenylthiosemicarbazone and isaTSC = anion of isatin-β-thiosemicarbazone) [31,46-48]. The bite angles within each ligand were smaller for N-Ni-O [79.98 and 80.49 °] than for N-Ni-S [80.74 and 81.07 °], all of which were comparable to those reported previously [31,46-48]. The coordination of the ligands to the metal ion via its enethiolate tautomeric form is evident from the elongation of the C3-S2 (1.713 Å) and C25-S24 (1.719 Å) bonds and shortening of the C3-N12 and C25-N34 bonds to 1.320 Å, compared with the free ligand. Although the crystal structure of **2a** is similar to that described in the literature, the crystal quality and parameter of this title compound is better (16,748 reflections were measured and 6,654 of them were observed at $I > 2\sigma(I)$) than those reported previously (for known structure of literature, only 3,805 reflections were measured and 1,449 of them were observed at $I > 2\sigma(I)$) [31]. Most importantly, the synthesis method is very different and no biological studies have yet been reported for this complex. Comparison of the nickel coordinate bond lengths between **2a** and the related Ni(II) complexes containing two tridentate N-O-$S_{thiolate}$ ligands, [Ni(isasbz)$_2$·DMSO], [Ni(isa-sme)$_2$·MeCN], [Ni(isaPhTSC)$_2$], [Ni(isaTSC)$_2$·2DMF] and [Ni(isaTSC)$_2$·EtOH] [31,46-48] demonstrates the similarity of these distances (**Table 3**).

Table 3 Ni-donor atom distances (Å) of N-O-$S_{thiolate}$ tridentate six coordinate Ni(II) complexes.

Compound	Bond type			Reference
	Ni-S	Ni-N	Ni-O	
2a	2.385 (7)	2.011 (18)	2.206 (17)	This work
	2.389 (7)	2.016 (18)	2.232 (18)	This work
[Ni(isasbz)$_2$·DMSO]	2.357	2.009	2.270	[31]
[Ni(isa-sme)$_2$·MeCN]	2.382, 2.385	1.995, 2.007	2.227, 2.294	[46]
[Ni(isaPhTSC)$_2$]	2.363, 2.364	2.013, 2.017	2.222, 2.275	[47]
[Ni(isaTSC)$_2$·2DMF]	2.345, 2.379	2.027, 2.021	2.178, 2.213	[48]
[Ni(isaTSC)$_2$·EtOH	2.368	2.023	2.226	[48]

Antimicrobial activity

Table 4 shows the antimicrobial activity result of the assayed compounds in which DMSO was employed as a negative control, illustrating the absence of any antimicrobial activity. Further to the above, standard antibiotic (streptomycin) and antifungal (nystatin) drugs were screened for comparison. **HL1** and its nickel(II) complex demonstrated no antimicrobial effects against all tested strains with no complete inhibition of microorganism growth. However, these strains were susceptible towards streptomycin and nystatin, indicating the validity of the assays performed. The cif file of complex **2a** obtained from the X-ray crystallography can further be used to perform molecular docking studies and theoretical calculations for ascertaining the enzyme or protein binding interaction mechanism, which might help to explain the lack of antimicrobial activity.

Table 4 Qualitative antibacterial assay.

	Inhibitory activity (mm)				
Microorganisms	**HL1**	**2**	**streptomycin**	**nystatin**	**DMSO**
MRSA	-	-	25	-	-
B. subtilis	-	-	15	-	-
P. aeruginosa	-	-	20	-	-
S. choleraesuis	-	-	17	-	-
C. albicans	-	-	-	23	-
A. ochraceous	-	-	-	24	-
S. cerevisiae	-	-	-	28	-

(-) indicates the absence of inhibitory activity

Conclusions

Isatin dithiocarbazate based nickel(II) complex was synthesized using acetate metal salt in an ethanolic solution without the exclusion of air or ambient moisture. The spectral and analytical data concluded that the ligand binds to the metal in a 1:2 (metal:ligand) stoichiometry in a distorted octahedral geometry. The crystal structure of **2a** confirms the suggested geometry in which the ligand was doubly deprotonated and chelated the Ni(II) ion in a di-ionic tridentate manner via neutral azomethine nitrogen, carbonylic oxygen and ionic sulfur of thiol. Both **HL1** and **Ni(SBISA)$_2$** were inactive against all microorganisms tested.

Acknowledgement

The authors gratefully acknowledge Ministry of Higher Education of Malaysia (MOHE) and Universiti Teknologi MARA, Malaysia for financial support (Grant number: 600-RMC/SRC/5/3 (043/2020).

References

[1] A Banerjee, M Mohanty, S Lima, R Samanta, E Garribba, T Sasamori and R Dinda. Synthesis, structure and characterization of new dithiocarbazate-based mixed ligand oxidovanadium(IV) complexes: DNA/HSA interaction, cytotoxic activity and DFT studies. *New J. Chem.* 2020; **44**, 10946-63.

[2] Y Gou, M Chen, S Li, J Deng, J Li, G Fang, F Yang and G Huang. Dithiocarbazate-copper complexes for bioimaging and treatment of pancreatic cancer. *J. Med. Chem.* 2021; **64**, 5485-99.

[3] A Santra, P Brandao, G Mondal, P Bera, A Jana, I Bhattacharyya, C Pramanik and P Bera. Monomeric and dimeric cadmium(II) complexes of S-alkyl/aryl dithiocarbazate as single-source precursors for cadmium sulfide nanoparticles: An experimental, theoretical interpretation in the stability of precursor and visible light dye degradation study. *Inorg. Chim. Acta* 2020; **501**, 119315.

[4] FU Rahman, SB Yu, SK Khalil, YP Wu, S Koppireddi, ZT Li, H Wang and DW Zhang. Chromone and benzyldithiocarbazate based probe: A highly selective and sensitive platform for colorimetric sensing of Cu^{2+}, single crystal of the complex and DFT calculations. *Sensor. Actuator. B Chem.* 2018; **263**, 594-604.

[5] A Santra, G Mondal, M Acharjya, P Bera, A Jana, SI Seok and P Bera. New pyrazole based single precursor for the surfactantless synthesis of visible light responsive PbS nanocrystals: Synthesis, X-ray crystallography of ligand and photocatalytic activity. *Nano Struct. Nano Object*. 2017; **10**, 91-9.

[6] MA Malik, SA Lone, MY Wani, MI Talukdar, OA Dar, A Ahmad and AA Hashmi. S-benzyldithiocarbazate imine coordinated metal complexes kill *Candida albicans* by causing cellular apoptosis and necrosis. *Bioorg. Chem.* 2020; **98**, 103771.

[7] WP Sohtun, T Khamrang, A Kannan, G Balakrishnan, D Saravanan, MA Akhbarsha, M Velusamy and M Palaniandavar. Iron(III) bis-complexes of Schiff bases of S-methyldithiocarbazates: Synthesis, structure, spectral and redox properties and cytotoxicity. *Appl. Organomet. Chem*. 2020; **34**, e5593.

[8] JK Bilyj, NV Silajew and PV Bernhardt. Nickel coordination chemistry of bis(dithiocarbazate) Schiff base ligands; metal and ligand centred redox reactions. *Dalton Trans*. 2021; **50**, 612-23.

[9] GF de Sousa, CC Gatto, IS Resck and VM Deflon. Synthesis, spectroscopic studies and X-ray crystal structures of new pyrazoline and pyrazole derivatives. *J. Chem. Crystallogr*. 2011; **41**, 401-8.

[10] A Abdildinova and YD Gong. Current parallel solid-phase synthesis of drug-like oxadiazole and thiadiazole derivatives for combinatorial chemistry. *ACS Comb. Sci*. 2018; **20**, 309-29.

[11] LH Al-Wahaibi, YS Mary, YS Mary, AA Al-Mutairi, HM Hassan, AA El-Emam and R Yadav. Investigation of the electronic properties of solvents (water, benzene, methanol) using IEFPCM model, spectroscopic investigation with docking and MD simulations of a thiadiazole derivative with anti-tumor activities. *J. Mol. Liq.* 2021; **348**, 118061.

[12] AM Younis, MM El-Gamil, TH Rakha and GM Abu El-Reash. Iron(III), copper(II), cadmium(II), and mercury(II) complexes of isatin carbohydrazone Schiff base ligand (H_3L): Synthesis, characterization, X-ray diffraction, cyclic voltammetry, fluorescence, density functional theory, biological activity, and molecular docking studies. *Appl. Organomet. Chem*. 2021; **35**, e6250.

[13] W Jamil, S Solangi, M Ali, KM Khan, M Taha and MY Khuhawar. Syntheses, characterization, *in vitro* antiglycation and DPPH radical scavenging activities of isatin salicylhydrazidehydrazone and its Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) metal complexes. *Arabian J. Chem*. 2019; **12**, 2262-9.
[14] MAFA Manan, MIM Tahir, KA Crouse, R Rosli, FNF How and DJ Watkin. The crystal structure and cytotoxicity of centrosymmetric copper(II) complex derived from S-methyldithiocarbazate with isatin. *J. Chem. Crystallogr*. 2011; **41**, 1866-71.
[15] MAFA Manan, MIM Tahir, KA Crouse and FNF How. Distorted octahedral S-methyl 2-(2-oxoindolin-3-ylidene) hydrazinecarbodithioate (SMISA) tridentate Schiff base complex of Co(II): Synthesis, characterization and structural studies. *Malaysian J. Chem*. 2020; **22**, 25-31
[16] R Mishra, H Chaurasia, VK Singh, F Naaz and RK Singh. Molecular modeling, QSAR analysis and antimicrobial properties of Schiff base derivatives of isatin. *J. Mol. Struct*. 2021; **1243**, 130763.
[17] G Singh, P Kalra, A Singh, G Sharma, C Espinosa-Ruíz and MA Esteban. A quick microwave preparation of isatin hydrazone schiff base conjugated organosilicon compounds: Exploration of their antibacterial, antifungal, and antioxidative potentials. *J. Organomet. Chem*. 2021; **953**, 122051.
[18] F Ramilo-Gomes, Y Addis, I Tekamo, I Cavaco, DL Campos, FR Pavan, CS Gomes, V Brito, AO Santos, F Domingues, Â Luís, MM Marques, JC Pessoa, S Ferreira, S Silvestre and I Correia. Antimicrobial and antitumor activity of S-methyl dithiocarbazate Schiff base zinc(II) complexes. *J. Inorg. Biochem.* 2021; **216**, 111331.
[19] H Guo. Isatin derivatives and their anti-bacterial activities. *Eur. J. Med. Chem*. 2019; **164**, 678-88.
[20] K Bajaj, RM Buchanan and CA Grapperhaus. Antifungal activity of thiosemicarbazones, bis(thiosemicarbazones), and their metal complexes. *J. Inorg. Biochem*. 2021; **225**, 111620.
[21] M Claudel, JV Schwarte and KM Fromm. New antimicrobial strategies based on metal complexes. *Chemistry* 2020; **2**, 849-99.
[22] SH Sumrra, AH Atif, MN Zafar, M Khalid, MN Tahir, MF Nazar, MA Nadeem and AA Braga. Synthesis, crystal structure, spectral and DFT studies of potent isatin derived metal complexes. *J. Mol. Struct*. 2018; **1166**, 110-20.
[23] M Shakir, N Bano, MA Rauf and M Owais. Pharmacologically significant tetraaza macrocyclic metal complexes derived from isatin and 3,4-diaminobenzophenone: Synthesis, spectral studies and comparative *in vitro* biological assessment. *J. Chem. Sci*. 2017; **129**, 1905-20.
[24] NK Singh, AA Kumbhar, YR Pokharel and PN Yadav. Anticancer potency of copper(II) complexes of thiosemicarbazones. *J. Inorg. Biochem*. 2020; **210**, 111134.
[25] EA Permyakov. Metal binding proteins. *Encyclopedia* 2021; **1**, 261-92.
[26] S Nath, R Pathania, G Grover and MJ Akhtar. Isatin containing heterocycles for different biological activities: Analysis of structure activity relationship. *J. Mol. Struct*. 2020; **1222**, 128900.
[27] OA Dar, SA Lone, MA Malik, FM Aqlan, MY Wani, AA Hashmi and A Ahmad. Synthesis and synergistic studies of isatin based mixed ligand complexes as potential antifungal therapeutic agents. *Heliyon* 2019; **5**, e02055.
[28] P Jain and V Singh. Pharmacological activity of newly synthesized and characterized N, O-donor tetraaza macrocyclic metal complexes. *Asian J. Pharm*. 2016; **10**, 612-22.
[29] E Vitaku, DT Smith and JT Njardarson. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among US FDA approved pharmaceuticals: Miniperspective. *J. Med. Chem*. 2014; **57**, 10257-74.
[30] MAF Abdul Manan. 2008, Synthesis, characterisation and biological activity screening of Schiff base ligands containing isatin and their metal complexes. Master Thesis. Universiti Putra Malaysia, Serdang, Malaysia.
[31] MA Ali, AH Mirza, JH Bakar and PV Bernhardt. Preparation and structural characterization of nickel(II), cobalt(II), zinc(II) and tin(IV) complexes of the isatin Schiff bases of S-methyl and S-benzyldithiocarbazates. *Polyhedron* 2011; **30**, 556-64.
[32] Z Otwinowski and W Minor. Processing of X-ray diffraction data collected in oscillation mode. *Meth. Enzymol*. 1997; **276**, 307-26
[33] A Altomare, G Cascarano, G Giacovazzo, A Guagliardi, MC Burla, G Polidori and M Camalli. SIRPOW. 92 - a program for automatic solution of crystal structures by direct methods optimized for powder data. *J. Appl. Cryst*. 1994; **27**, 435-6.
[34] DJ Watkin, CK Prout, JR Carruthers and PW Betteridge. *CRYSTALS. Issue 10*. Chemical Crystallography Laboratory, University of Oxford, Oxford, England, 1996.
[35] CF Macrae, I Sovago, SJ Cottrell, PT Galek, P McCabe, E Pidcock, M Platings, GP Shields, JS Stevens, M Towler and PA Wood. *Mercury 4.0*: From visualization to analysis, design and prediction. *J. Appl. Crystallogr*. 2020; **53**, 226-35.

[36] AW Bauer. Antibiotic susceptibility testing by a standardized single disk method. *Am. J. Clin. Pathol*. 1966; **45**, 493-6.
[37] NP Peet and RJ Barbuch. Mass spectral fragmentation and rearrangement of isatin derivatives. *Org. Mass. Spectrom.* 1984; **19**, 171-5.
[38] FC Lima, YA Só, R Gargano, DM de Oliveira and CC Gatto. Structural, theoretical and biological activity of mono and binuclear nickel(II) complexes with symmetrical and asymmetrical 4,6-diacetylresorcinol-dithiocarbazate ligands. *J. Inorg. Biochem*. 2021; **224**, 111559.
[39] Z Yekke-ghasemi, M Ramezani, JT Mague and R Takjoo. Synthesis, characterization and bioactivity studies of new dithiocarbazate complexes. *New J. Chem*. 2020; **44**, 8878-89.
[40] M Enamullah, MA Zaman, MM Bindu, MK Islam and MA Islam. Experimental and theoretical studies on isatin-Schiff bases and their copper (II)-complexes: Syntheses, spectroscopy, tautomerism, redox potentials, EPR, PXRD and DFT/TDDFT. *J. Mol. Struct*. 2020; **1201**,127207.
[41] CA Wegermann, E Monzani, L Casella, MA Ribeiro, CE Bruzeguini, JD Vilcachagua, LA Costa and AM Ferreira. Unveiling geometrical isomers and tautomers of isatin-hydrazones by NMR spectroscopy. *J. Mol. Struct*. 2022; **1250**, 131633.
[42] ES El-Samanody, SA AbouEl-Enein and EM Emara. Molecular modeling, spectral investigation and thermal studies of the new asymmetric Schiff base ligand; *(E)-N′-(1-(4-((E)-2-*hydroxybenzylideneamino)phenyl)ethylidene)morpholine-4-carbothiohydrazide and its metal complexes: Evaluation of their antibacterial and anti-molluscicidal activity. *Appl. Organomet. Chem*. 2018; **32**, e4262.
[43] HF Abd El-Halim, FAN El-Dien, GG Mohamed and NA Mohamed. Chelating behavior, thermal studies and biocidal efficiency of tioconazole and its complexes with some transition metal ions. *J. Therm. Anal. Calorim*. 2013; **111**, 173-181.
[44] JR Anacona, VE Marquez and Y Jimenez. Synthesis and characterization of manganese(II), nickel(II), copper(II) and zinc(II) Schiff-base complexes derived from 1,10-phenanthroline-2,9-dicarboxaldehyde and 2-mercaptoethylamine. *J. Coord. Chem*. 2009; **62**, 1172-9.
[45] WJ Geary. The use of conductivity measurements in organic solvents for the characterisation of coordination compounds. *Coord. Chem. Rev*. 1971; **7**, 81-122.
[46] MA Ali, JH Bakar, AH Mirza, SJ Smith, LR Gahan and PV Bernhardt. Preparation, spectroscopic characterization and X-ray crystal and molecular structures of nickel(II), copper(II) and zinc(II) complexes of the Schiff base formed from isatin and S-methyldithiocarbazate (Hisa-sme). *Polyhedron* 2008; **27**, 71-9.
[47] C Balachandran, J Haribabu, K Jeyalakshmi, NS Bhuvanesh, R Karvembu, N Emi and S Awale. Nickel(II) bis(isatin thiosemicarbazone) complexes induced apoptosis through mitochondrial signaling pathway and G0/G1 cell cycle arrest in IM-9 cells. *J. Inorg. Biochem*. 2018; **182**, 208-21.
[48] MC Rodríguez-Argüelles, A Sánchez, MB Ferrari, GG Fava, C Pelizzi, G Pelosi, R Albertini, P Lunghi and S Pinelli. Transition-metal complexes of isatin-β-thiosemicarbazone. X-ray crystal structure of two nickel complexes. *J. Inorg. Biochem*. 1999; **73**, 7-15.